NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence: MT288

Evaluation title: The XprESS Multi-Sinus Dilation System for the treatment of chronic rhinosinusitis

Sponsor: Entellus Medical, Inc.

Date sections A and B submitted: February 15, 2016

Date section C submitted: To be submitted separately

March 2013

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Glossary of terms

Term	Definition
CRS	Chronic rhinosinusitis
FDA	Food and Drug Administration (United States)
FESS	Functional endoscopic sinus surgery
IFU	Instructions for use
RSI	Rhinosinusitis Symptom Inventory
SN-5	Sinus and Nasal Quality of Life Survey
SNOT-20 or -22	Sino-Nasal Outcome Test (20 or 22 item)
WLQ	Work Limitation Questionnaire
WPAI	Work Productivity and Activity Impairment questionnaire

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medication Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1-1. Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People with chronic rhinosinusitis, including recurrent acute rhinosinusitis, in whom all medical therapy has failed.	None	NA
Intervention	The XprESS Multi-Sinus Dilation System	None	NA
Comparator(s)	• Functional endoscopic sinus surgery (FESS) • Other balloon sinus dilation systems available in the NHS (see also 'Cost analysis' below)	None	NA
Outcomes	The outcome measure to consider include: *Patient outcomes:* • Change in rhinosinusitis symptoms (Sinus nasal outcome test [SNOT version 20 or 22] or rhinosinusitis symptom inventory [RSI]) • Number of post-procedure rhinosinusitis episodes requiring medication • Number of post-operative debridements • Change in ostial patency (assessment of sinus drainage pathway patency by endoscopy or CT scan) • Duration of analgesic medication • Patient-reported tolerance of the procedure and/or patient reported severity of pain scale • Number and types of sinuses treated *Health care system outcomes:* • Length of hospital stay • Procedure time and theatre/outpatient treatment room time • Success rates of maxillary sinus ostial	None	NA

	Scope issued by NICE	Variation from scope	Rationale for variation
	cannulation • Rate of revision surgery • Number of sinus-related follow-up appointments • Rate of readmission • Numbers and grade of staff required *Adverse effects:* • Rate and severity of nasal bleeding • Device-related adverse events		
Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters which will consider scenarios in which different staff, treatment facilities (hospital theatre vs day-case), and methods of anaesthesia are needed.	None	NA
Subgroups to be considered	• Patients with uncomplicated chronic rhinosinusitis (or uncomplicated recurrent acute rhinosinusitis) • Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) with orbital or intracranial involvement • Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) with and without nasal polyps • Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) affecting the anterior ethmoid sinus in addition to maxillary, frontal or sphenoidal sinus disease • Patients with anatomic variants such as septal deviations and accessory ostia • Children and young people under 18 years of age	No data is provided for patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) **with orbital or intracranial involvement**	These patients are most likely to undergo FESS and were not enrolled in any of the standalone balloon studies.
Special considerations, including issues related to equality	No equality issues have been identified. The XprESS Multi-Sinus Dilation System may be a suitable alternative to FESS for patients who are unable or unwilling to tolerate general anaesthetic.	None	NA

2 Description of technology under assessment

The XprESS Multi-Sinus Dilation System is a sterile, single-use system device for treating chronic rhinosinusitis. The system comprises a balloon-tipped device with a reshapable end that is inserted through the nose into the maxillary, frontal, or sphenoid sinuses. The XprESS system

also includes an inflation syringe, bending tool, and 2 extension lines to provide irrigation. The balloon is manipulated into the bony sinus outflow tracts (ostia) and inflated with saline to dilate and remodel them by displacing adjacent bone and paranasal sinus structures. This allows the sinuses to drain more effectively. The XprESS system comes in 3 variations: the XprESS Ultra, XprESS LoProfile, and the XprESS Pro. These differ in the dimensions of the suction tip and the balloon diameter and length; selection is based on clinician preference. The XprESS device, inflation syringe, and bending tool are included in all 3 variations. The Ultra and LoProfile (the version sold in the UK) also include an integrated PathAssist LED Light Fiber, which is available as an add-on for the Pro. The XprESS procedure can be performed under local anaesthesia, once the surgeon has had sufficient experience using the device.

3 Clinical content

3.1 Disease overview

Chronic rhinosinusitis (CRS) is a complex disorder that involves inflammation of the mucosal tissue that lines the sinuses and causes symptoms that persist (for 12 weeks or longer) or reoccur (4 or more times in 1 year; recurrent acute rhinosinusitis). [Rosenfeld, et al. 2015; Fokkens, et al. 2012].

Causes of CRS include allergic reactions, infections, and environmental irritants that induce inflammation of the mucosal tissues. This inflammation in turn inhibits mucus drainage, increases pressure in the sinuses, and contributes to further infections. Symptoms include mucopurulent drainage, nasal obstruction, facial pain/pressure/fullness, and decreased sense of smell.

The condition significantly reduces work productivity, increases absenteeism, impairs daily activities and is associated with high health care utilisation. In the UK, the incidence of CRS is a highly prevalent condition affecting 10% of the UK adult population. [Commissioning guide: ENTUK 2013]. Approximately 213,000 UK patients per year are referred to sinus surgery (FESS) and approximately 32,500 FESS procedures are completed annually [UK validation HSCIC HES data, April 2013 to March 2014]. There is over a 5 fold variation in procedure rates for sinus surgery per 100,000 population by CCG across England [Commissioning guide: ENTUK 2013].

3.2 NICE or other national guidelines or expert guidelines for condition of use

There has been no previous evaluation specific to the XprESS Multi-Sinus Dilation System. A NICE interventional procedure guidance was published in September 2008 for balloon dilation procedures: IPG 273 “Balloon catheter dilation of paranasal sinus ostia for chronic sinusitis”.

3.3 Clinical pathway of care

Medical treatment regimens involving antibiotics and anti-inflammatory medications (corticosteroids) are the first-line treatment options for chronic rhinosinusitis. Due to frequently recurring sinus infections, many patients undergo multiple regimens of antibiotic therapy, often starting with amoxicillin or Augmentin and then progressing to cephalosporins, macrolides,

and/or quinolone antibiotic therapy. Since medical therapy does not address the underlying anatomical issues contributing to the disease, medical treatment alone does not satisfactorily resolve all symptoms for some patients. When chronic rhinosinusitis symptoms persist or recur frequently despite ongoing or progressive medical management to control the underlying inflammatory disease, functional endoscopic sinus surgery (FESS) or balloon dilation is commonly performed.

The therapeutic intent of FESS and balloon dilation is to improve patient quality of life through relief of persistent symptoms by enlarging the natural drainage pathways (ostia) of the affected sinuses to restore mucus flow and ventilation. For FESS, tools such as microdebriders and curettes are introduced through the nose to remove the diseased tissue and open up or expand these drainage pathways. Because bone and tissue are removed during FESS, the procedures are routinely performed under general anesthesia and may be accompanied by an extended recovery time. In contrast, balloon dilation remodels the bony structures of the ostia without cutting or removal of tissue and can be performed under local anesthesia with rapid recovery times.

To facilitate wound healing and minimize postoperative scarring and stenosis, after FESS a series of postsurgical follow-up debridement procedures are often required to remove crusting. These are rarely required following balloon dilation procedures.

Complications associated with FESS may include orbital hematoma, damage to intraorbital structures, loss of vision, cerebrospinal fluid leak, and damage to intracranial structures [Stammberger. 1990]. Over the last decade, imaging technology enhancements and powered surgical instruments have helped improve the precision of surgical dissection, reduce tissue trauma, and promote quicker postoperative recovery [Cohen. 2005]. Complications associated with balloon dilation are theoretically similar to those associated with FESS; however, they occur less often.

3.4 Current clinical practice issues

Currently, CRS patients who have failed maximum medical management are referred to the specialist community/ENT Consultant for FESS. FESS is typically performed in a operating theatre with the patient under general anesthesia. Although FESS is designed to preserving the mucosa and cilia lining of the sinuses as much as possible, it remains an invasive procedure. After FESS, patients usually return to normal daily activities within 7 to 14 days. Additional office visits and debridement procedures are frequently required after FESS to ensure appropriate healing occurs.

3.5 New pathway of care for new technology

The clinical practice and pathway of care for the XprESS Multi-Sinus Dilation System is similar to that of FESS in that the CRS patient who has failed maximum medical management would be referred to the specialist community/ENT Consultant surgeon to perform the procedure on the appropriate sinus(es). When standalone balloon dilation procedures are performed on the maxillary, frontal or sphenoid sinus ostia, they will replace the corresponding FESS procedure for the particular sinus(es).

In contrast to FESS, balloon sinus dilation is easily performed under local anesthesia in a day theatre setting. The procedure is minimally invasive with patients typically returning to normal daily activities within 1 to 2 days. Debridement procedures are rarely required after balloon sinus dilation and patients require postoperative prescription pain medications for shorter durations than those who undergo FESS.

3.6 Changes to organisation of current services

Balloon sinus dilation can be utilized in both the operating theatre or day surgical and surgical ambulatory facilities. Patients who are currently treated under general anaesthesia in operating theatres could alternatively undergo treatment in a surgical day-case ambulatory care setting under local anaesthesia. Such day-case facilities are currently available in NHS hospitals and are typically under utilised. Where surgeons prefer to perform the XprESS procedure in operating theatres under general anaesthesia, XprESS is still more efficient and offers economic advantages over FESS, such as shorter procedure times, shorter lengths of stay, and quicker recovery times. Day-case facilities would need to be made available to ENT surgeons wishing to use the XprESS system in such settings, if adoption of this technology was supported.

3.7 Additional tests or investigations needed

None known.

3.8 Additional facilities, technologies, or infrastructure needed

Additional facilities, technologies, or infrastructure is not needed. The day-case ambulatory care surgical facilities already exist in NHS hospitals and are currently under utilised.

3.9 Tests, investigations, interventions, facilities, or technologies no longer needed

None known.

3.10 How can NHS divest from items listed in Section 3.9?

Not applicable.

4 Regulatory information

4.1 PDF documents

PDF copies of the following documents are provided as Attachments 1 through 3 to this report.

- Instructions for use (IFU)
- CE mark certificate
- ISO 13485 certificate

4.2 Does technology have CE mark for the indication?

The XprESS Multi-Sinus Dilation System received CE mark in October 2010. According to the Medical Device Directive 93/42/EEC, Annex IX, Rule 6, the XprESS Multi-Sinus Dilation System is a Class IIa medical device.

4.3 Does the technology have regulatory approval outside the UK?

The XprESS Multi-Sinus Dilation System was cleared for marketing by the US FDA through the 510(k) process in October 2010. The device is also approved for marketing in the European Union (currently being sold in the UK, Finland, France, Italy, Poland, Portugal, and Spain), Australia, Canada, and Malaysia.

4.4 If the technology has not been launched in the UK, provide the anticipated date of availability

Not applicable.

4.5 If technology has been launched in the UK, provide information on use in England

The following physicians are using the XprESS Multi-Sinus Dilation System in their clinical practice:

Institution	**Clinicians**
Guys and St Thomas University NHS Trust	Mr. David Roberts Miss Claire Hopkins
UCL University NHS Trust - RNTNE	Mr. Peter Andrews
Croydon University NHS Trust	Mr. Ben Hunter
Frimley Park Hospital NHS Trust	Mr. Johnathan Hern
Lewisham Hospital NHS Trust	Mr. Nabil Salama Mr. Irfan Syed
James Padget University NHS Trust	Mr. Carl Philpott
St. George's University NHS Trust	Mr. Abbad Toma Ms. Sarah Little
Lister Hospital and Chorley Hospital, Chorley and South Ribble NHS Trust	Mr. John De Carpentier
Manchester Royal Infirmary	Mr. Atef El Kholy
Brighton NHS Trust	Mr. Michael O'Connell
Central Middlesex	Mr. Arvind Singh

5 Ongoing studies

5.1 Completed and ongoing studies on the technology

Entellus Medical has sponsored 7 completed clinical studies of the XprESS and FinESS devices for treatment of CRS. The FinESS device was the first of the Entellus balloon dilation devices and has been obsoleted in favor of the XprESS device. The only difference between the devices is the approach: FinESS is placed through a transantral approach versus the transnasal approach of the XprESS device. The transnasal approach is the preferred approach due to its being more versatile and less invasive that the transantral approach. A review of historical outcome data (SNOT-20 scores) by an independent statistician confirmed that the FinESS and XprESS data were poolable and that the method of access to the sinus does not affect poolability. Therefore, the results of the FinESS clinical studies are considered relevant to the assessment of the XprESS device and are included in the evaluation of clinical evidence as an "equivalent" device.

The results of 5 of the Entellus Medical studies have been published in 11 peer-reviewed journal articles and the results of 1 pilot study was published as a white paper (not peer-reviewed). Six of the studies were evaluated in a meta-analysis of participant-level data that was published in a peer-reviewed journal (Section 7.8). The clinical evidence from these studies is presented in Section 7.

Entellus Medical has completed a clinical study of the XprESS device in pediatric CRS patients. Publication of the results of the pediatric study is expected in 2016.

5.2 Is technology subject to any other form of assessment in the UK?

The XprESS Multi-Sinus Dilation System is not currently under any other form of assessment in the UK.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1 Describe equality issues related to patient population and condition

None are known at this time.

6.2 Describe equality issues related to the assessment of the technology

None are known at this time.

6.3 How will the submission address these issues?

The submission does not address equality since there are no known equality issues associated with the patient population, condition, technology, or procedure.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B required sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods fuide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in Table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timeline, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

7.1.1 Published studies

A systematic literature search was conducted using the following databases and parameters:

Search databases: Medline (via OVID), Medline (via Pubmed), Embase (via OVID), Cochrane Database of Systematic Reviews (via Wiley)
Search date: December 29, 2015
Search date span: 2006 to December 29, 2015
Inclusion criteria: English language, Human studies
Exclusion criteria: case reports, editorials, letters, review articles, books, technology assessment reviews, modeling/bench/non-human studies, false hits
Search strategies:

Terms	Results
Medline (via OVID)	
exp Sinusitis OR (sinusitis OR rhinosinusitis).af	22,373
exp Dilatation, Pathologic OR ((dilat* or balloon* or catheter* or sinuplast*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier])	415,977
Sinusitis terms AND dilatation terms	392
Limits: English, Human, 2006 to present	**160**
Embase (via OVID)	
exp sinusitis OR exp rhinosinusitis	37,053
exp balloon catheter/ OR exp balloon dilatation/ OR ((dilat* or balloon* or catheter*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]) OR (sinuplast*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword])	593,554
Sinusitis terms AND dilatation terms	778

Terms	Results
Medline (via OVID)	
Limits: English, Human, 2006 to present, remove Medline	**58**
Medline (via Pubmed)	
("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*) AND ("Sinusitis"[Mesh] OR sinusitis OR rhinosinusitis OR sinuplast*) AND (Limits: English, Human, 2006-present)	**172**

Search results:
Total number of references downloaded: 390
Total number of evaluated references after de-duplication: 229
Review articles: 30
Technology Assessment articles: 3
Rejected references (exclusion criteria): 126
Total number of references for review: 70

Seventy titles and abstracts identified through the literature search were reviewed and articles were selected for further consideration based on the criteria listed in Table B7-1. Three other relevant articles were identified separately and included in the analysis.

Articles were excluded from the analysis if they were editorials, reviews, position or policy papers, practice guidelines, or did not provide clinical safety or performance data for the indicated use (eg, bench or animal data, off-label uses).

7.1.2 Unpublished studies

Two unpublished studies were identified internally from completed studies sponsored by Entellus Medical that have not been published in peer-reviewed journals. A registry study of the FinESS device was not published as a separate study but data from the study was included in the meta-analysis reported by Chandra et al (2016).

A multicenter, single-arm study of the XprESS device in pediatric CRS patients was conducted. Publication of the study results is expected in 2016.

[redacted]

7.2 Study selection

7.2.1 Published studies inclusion and exclusion criteria

Selection criteria for the published and unpublished studies are listed in Table B7-1.

Table B7-1. Selection criteria for published and unpublished studies

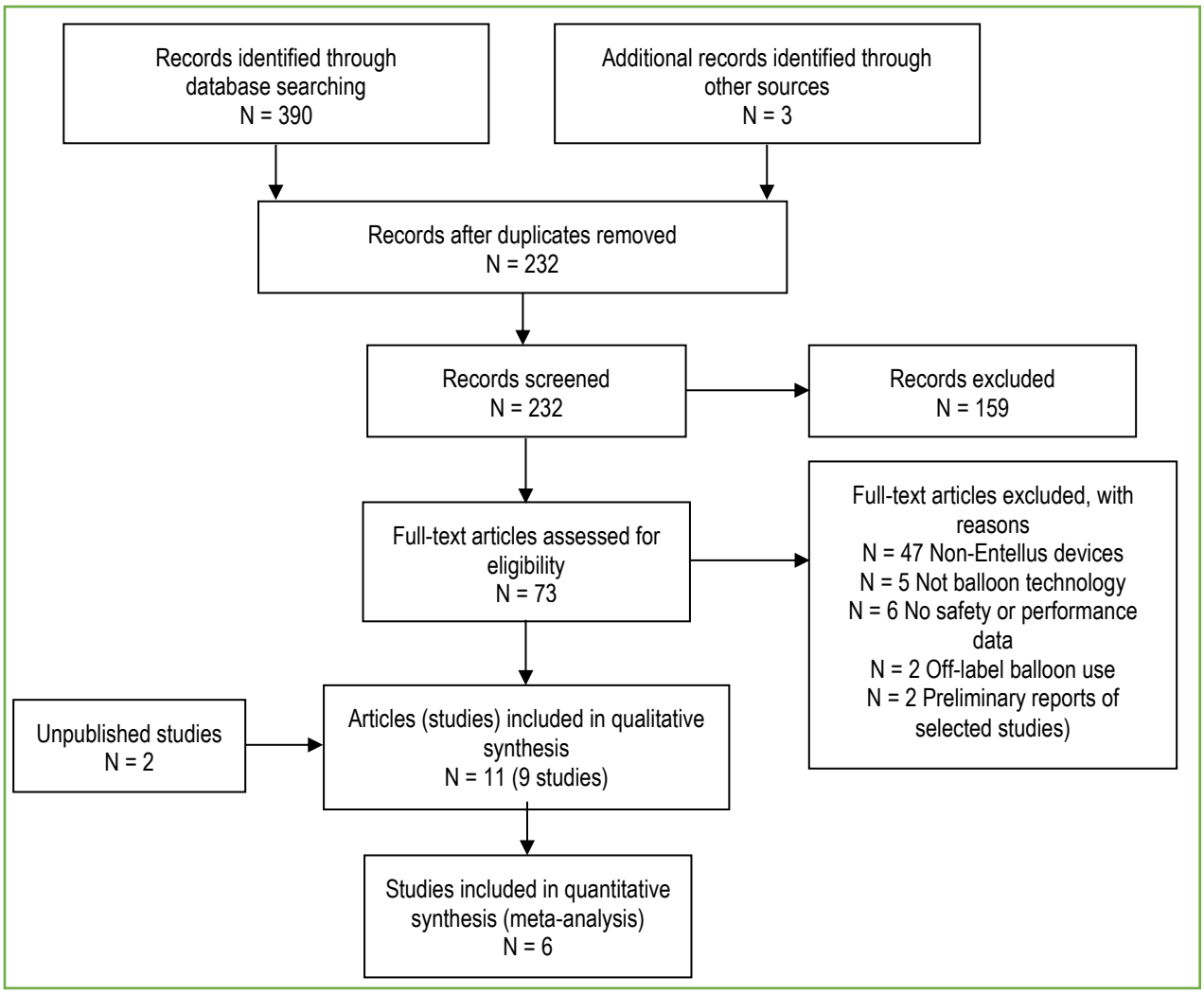
Inclusion criteria	
Population	Patients with chronic rhinosinusitis
Interventions	Balloon sinus dilation using the XprESS Multi-Sinus Dilation System or equivalent. Functional endoscopic sinus surgery (FESS) (comparator intervention)
Outcomes	Technical success, sinus symptom improvement, debridement rate, revision surgery rate, recovery outcomes, healthcare utilization, work productivity, ostial patency rate, procedure pain, and complications.
Study design	Meta-analysis, randomized controlled trial, observational case series, comparative case series, retrospective chart reviews, case reports

Language restrictions	English
Search dates	2006 to present
Exclusion criteria	
Population	Patients with conditions other than chronic rhinosinusitis, cadaver studies, non-human studies
Interventions	Balloon sinus dilation with products other than the XprESS and FinESS devices or unspecified balloon dilation devices Off-label uses of the XprESS or FinESS devices Sinus procedures not involving balloon technology
Outcomes	Outcomes not related to the efficacy or safety of balloon sinus dilation (incidental use of balloon dilation in a study with an unrelated objective)
Study design	Insurance claims database analyses, technology assessments, medical policy statements, reviews, commentary, letter to the editors
Language restrictions	Non-English
Search dates	Before 2006

7.2.2 Published studies selection flow

The process flow for the study search and selection for both published and unpublished studies is presented in Figure B7-1.

Figure B7-1. Studies selection flow



7.2.3 Unpublished studies inclusion and exclusion criteria

The selection criteria for the unpublished studies are identical to those listed for the published studies in Table B7-1.

7.2.4 Unpublished studies selection flow

Due to the small number of unpublished studies and the same selection criteria used, the unpublished studies are included with the published study selection flow in Figure B7-1.

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about the future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

Copies of the selected study publications listed in Table B7-2 are provided in Attachment 4 of this application. Structured abstracts of the 2 unpublished studies are provided in Attachment 5.

7.3.1 Details of selected studies

The general populations studied, intervention, and comparator for each selected study are outlined in Table B7-2 and Table B7-3.

Table B7-2. List of relevant published studies

Primary study reference	Study name (acronym)	Follow-up timeframe	Population	Intervention	Comparator
Chandra RK. 2016	REMODEL Larger cohort and Meta-analysis	Up to 2 years	Patients with CRS	Balloon sinus dilation with XprESS or equivalent	FESS
Bikhazi N. 2014	REMODEL	12 Months	Patients with CRS	Balloon sinus dilation with XprESS or equivalent	FESS
Cutler J. 2013	REMODEL	6 Months	Patients with CRS	Balloon sinus dilation with XprESS or equivalent	FESS
Gould J. 2014	XprESS Multi-Sinus Study	12 Months	Patients with CRS	Balloon sinus dilation with XprESS	Baseline
Brodner D. 2013	XprESS Registry	1 Month for all, 1 Year for a subset	Patients with CRS	Balloon sinus dilation with or without concomitant FESS (hybrid procedure)	Baseline
Gould JD. 2012[a]	XprESS Maxillary Pilot Study	6 Months	Patients with CRS	Balloon sinus dilation with XprESS	Baseline
Eloy JA. 2012	Retrospective case series	4 to 6 Months	Patients who had failed frontal sinusotomy	Balloon sinus dilation with XprESS	Baseline
Levine SB. 2013	RELIEF Study	12 Months	Patients with CRS	Balloon sinus dilation with XprESS equivalent device	Baseline
Stankiewicz J. 2012	BREATHE Study	2 Years	Patients with CRS	Balloon sinus dilation with XprESS equivalent device	Baseline
Cutler J. 2011	BREATHE Study	12 Months	Patients with CRS	Balloon sinus dilation with XprESS equivalent device	Baseline
Stankiewicz J. 2011	BREATHE Study	12 Months (Work productivity)	Patients with CRS	Balloon sinus dilation with XprESS equivalent device	Baseline

[a] Published as a white paper in the *ENT Journal* (not peer-reviewed).

Table B7-3. List of relevant unpublished studies

Primary study reference	Study name (acronym)	Follow-up timeframe	Population	Intervention	Comparator
Entellus Medical Internal Data, 2011	FinESS Registry	12 Months	Patients with CRS	Balloon sinus dilation with XprESS equivalent device	Baseline
Soler ZM. (publication expected in 2016)	Sinus Balloon Dilation in Pediatric Patients	6 Months	Pediatric patients (2-21 years) with CRS	Balloon sinus dilation with XprESS	Baseline

7.3.2 Rationale for exclusion of published studies

After full text review against the selection criteria noted in Table B7-1, a total of 62 of the 73 articles were excluded from analysis. Of the 62, 47 articles reported balloon sinus dilation using non-Entellus Medical devices or unspecified balloon devices. Five articles reported on outcomes from non-balloon sinus dilation technologies (eg, Vent-Os, steroid-eluting stents). Six articles did not report any safety or performance data for balloon sinus dilation. Two articles reported off-label uses of Entellus balloon devices; neither reporting any safety issues.

Lastly, 2 early publications of the BREATHE study were excluded from the analysis of selected studies because the results were limited to the first 30 participants enrolled.[Stankiewicz J, et al. 2009 and 2010] The later publications of the 1-year and 2-year outcomes for the full cohort of participants are included in this report.[Stankiewicz J, et al. 2011 and 2012; Cutler J, et al. 2011] Results from the first 30 participants were not appreciably different from the full cohort results.

7.4 Summary of methodology or relevant studies

A total of 11 articles were selected that represent results from 7 relevant studies of balloon sinus dilation using the Entellus Medical devices. In addition, the results from 2 unpublished clinical studies of the Entellus devices are included in the analysis.

7.4.1 Study design and methodology of selected studies

The tables below outline the design and methodology of the selected studies.

Table B7-4. Summary of methodology for randomized studies (REMODEL)

Study name	**REMODEL (Chandra RK, et al. 2016; Bikhazi N, et al. 2014; Cutler J, et al. 2013) NCT01525849**
Objectives	The 2 primary objectives of the REMODEL trial were: 1. to demonstrate that long-term symptom improvement after balloon dilation is not worse than symptom improvement after FESS (noninferiority), and 2. to show that fewer postoperative debridements are required after balloon dilation than after FESS (superiority).
Location	14 US centers
Design	Prospective, multicenter, unblinded, randomized controlled trial
Duration of study	Minimum of 12-months
Sample size	A sample size of 72 participants (36/arm) completing 12-month follow-up was required to obtain 90% power with a 1-sided alpha of 0.025 for the first primary objective.
Inclusion criteria	Adult (≥18 years) patients with CRS according to the 2007 AAO-HNS adult sinusitis clinical practice guidelines and meeting the Anthem or BlueCross BlueShield of North Carolina criteria for medically necessary FESS. Maxillary sinus disease with or without anterior ethmoid sinus disease.
Exclusion criteria	Patients with posterior ethmoid, sphenoid, or frontal sinus disease; fungal sinusitis; severe deviated septum; gross sinonasal polyposis; previous sinus surgery; nasal surgery within 3 months of randomization; requires any concomitant sinus surgery; ciliary dysfunction; Samter's triad; undergoing chemotherapy in the head/neck region; or pregnant.
Method of randomization	Treatment assignments were randomly generated by an independent statistician using a distribution in variable blocks sizes with an allocation of 1:1 of FESS to balloon dilation for each investigational center. The statistician placed treatment assignments in sequentially numbered and sealed envelopes that were maintained by the study sponsor. Participants were ready for treatment assignment after they had completed informed consent, been screened and evaluated for the inclusion and exclusion criteria, and completed all preprocedure evaluations except the pregnancy test, when applicable. When the center was ready to randomize a participant, they would contact the sponsor who would open the next assigned envelope for that

Study name	REMODEL (Chandra RK, et al. 2016; Bikhazi N, et al. 2014; Cutler J, et al. 2013) NCT01525849
	center and inform the center of the treatment assignment for that participant. The clinical centers' staff, treating physician, and sponsor personnel were blinded to the randomization scheme and the block sizes.
Method of blinding	The trial was unblinded because the balloon dilation participants were treated in the office under local anesthesia while the FESS participants were primarily treated in the operating theatre under general anesthesia. Despite the nonblinded study design, steps were taken to reduce the bias of the outcome reporting. An independent physician who was blinded to treatment assignment reviewed postoperative debridement details for consistency. Two additional independent physicians conducted an audit of the original case report forms (CRFs), data management processes, and quality control measures to verify data outputs and results accurately reflected the CRFs received from the investigators. Independent statisticians performed the statistical analyses.
Interventions (n=) and comparators (n=)	74 Balloon sinus dilation participants (XprESS or equivalent) 61 FESS (control) participants
Baseline differences	There were no significant differences between treatment groups with respect to any baseline characteristics including sex, age, race, smoking history, asthma, allergies, previous sinus surgery, septal deviations, SNOT-20 score, Lund-MacKay score, anterior ethmoid disease, and duration of sinus disease.
Duration of follow-up, lost to follow-up information	The minimum required follow-up was 12 months: 130/135 (96%) treated participants completed the 12-month follow-up, additionally, 66/66 (100%) participants completed 18-month follow-up and 25/25 (100%) participants completed 24-month follow-up.
Statistical tests	One-sided Student t-test for inferiority for primary endpoint of sinus symptom improvement. One-sided Student t-test for superiority for number of postoperative debridements per participant. Two-sided Student t-tests (normal distribution) or Wilcoxon Rank Sum tests (non-normal distribution) were used for continuous variable secondary endpoints and Fisher's exact test was used for categorical variable secondary endpoints. Benjamini-Hochberg correction was used to adjust the alphas for multiple comparisons for the secondary objectives.
Primary outcomes (including scoring methods and timing of assessments)	Noninferiority of balloon dilation to FESS for improvement of sinus symptoms (SNOT-20 score) at 6 and 12 months. Superiority of balloon dilation to FESS for the number of postoperative debridements per participant.
Secondary outcomes (including scoring methods and timing of assessments)	<u>Postoperative/short-term secondary outcomes:</u> Technical success Short-term sinus symptom improvement (SNOT-20) Recovery time Recovery outcomes <u>Long-term secondary outcomes (12 months):</u> Complications Revision rate Work productivity Reduction in rhinosinusitis episodes Ostial patency (by CT scan)

Table B7-5. Summary of methodology for observational studies (XprESS Multi-Sinus)

Study name	XprESS Transnasal Maxillary Multi-Sinus Study (Gould J, et al. 2014) NCT01612780
Objectives	Assess 1-year changes in sinonasal symptoms and health care use after office-based multisinus balloon dilation
Location	10 US centers
Design	Prospective, multicenter, single-arm study
Duration of study	12 months

Study name	XprESS Transnasal Maxillary Multi-Sinus Study (Gould J, et al. 2014) NCT01612780
Patient population	Adult CRS patients
Sample size	19 participants were adequate to test the hypothesis of a clinically meaningful difference of 0.8 in the SNOT-20 score using a 1-sided alpha of 0.25 and 90% power. Actual sample size was increased to allow for subgroup analyses.
Inclusion criteria	Adults (≥18 years) with CRS according to the 2007 AAO-HNS adult sinusitis clinical practice guidelines who had failed medical management. All participants were required to have maxillary sinus disease at a minimum.
Exclusion criteria	Previous maxillary sinus surgery; nasal surgery within 3 months; requires concomitant sinus or nasal surgery other than turbinate reduction; fungal sinus disease.
Interventions (n=) and comparators (n=)	82 participants underwent transnasal balloon dilation with the XprESS device under local anesthesia in an office setting. The baseline assessment for each participant served as the comparator.
Baseline differences	NA, each participant served as their own control.
How were participants followed-up? Duration of follow-up, lost to follow-up information	Proactive follow-up to 12 months post procedure. 77 of the 81 treated participants (94%) completed the 12-month follow-up.
Statistical tests	Fisher's exact tests (categorical variables) or 2-sided Student t-tests (continuous variables).
Primary outcomes (including scoring methods and timing of assessments)	Change in sinonasal symptom severity (SNOT-20 score) between baseline and follow-up.
Secondary outcomes (including scoring methods and timing of assessments)	Short term: Technical success Procedure tolerance Long-term (12 months): Change in symptoms and health care utilization (Rhinosinusitis Symptom Inventory) Adverse events Revision rate Preplanned subgroup analyses by sinus(es) treated, CRS diagnosis, baseline LM score, presence or absence of ethmoid disease, presence or absence of septal deviation, and presence or absence of turbinate hypertrophy.

Table B7-6. Summary of methodology for observational studies (XprESS Registry)

Study name	XprESS Registry (Brodner D, et al. 2013) NCT01115309
Objectives	Assess the safety and sustained effectiveness of balloon sinus dilation using the XprESS device in multiple sinuses.
Location	8 US centers
Design	Prospective, multicenter, registry study
Duration of study	1-month follow-up for all participants 1-year follow-up for the first 50 participants enrolled
Patient population	Adult CRS patients
Sample size	Not specified
Inclusion criteria	Adults (≥18 years) with CRS who were previously scheduled to undergo FESS.
Exclusion criteria	Ciliary dysfunction; cystic fibrosis; Samter's triad; hemophilia; immunosuppression; or undergoing radiation in the head/neck region.
Interventions (n=) and comparators (n=)	175 participants underwent transnasal balloon dilation with the XprESS device as a standalone or hybrid procedure. The baseline assessment for each participant served as the comparator.
Baseline differences	NA, each participant served as their own control.
How were participants followed-up? Duration of	Proactive follow-up to 1 month for all participants and to 12 months post procedure for the first 50 participants enrolled: 170/175 participants (97%) completed the 1-month visit, 44/50 long-

Study name	XprESS Registry (Brodner D, et al. 2013) NCT01115309
follow-up, lost to follow-up information	term participants (88%) completed the 12-month visit.
Statistical tests	2-sample t-tests (continuous variables). Nonparametric methods were used when appropriate.
Primary outcomes (including scoring methods and timing of assessments)	Serious device or procedure-related adverse events
Secondary outcomes (including scoring methods and timing of assessments)	Short-term follow-up outcomes: Technical success Anesthesia and fluoroscopy times Sinus symptom severity (SNOT-20) 12-month follow-up outcomes: Sinus symptom severity (SNOT-20) Ostial patency Revision rate

Table B7-7. Summary of methodology for unpublished observational studies (XprESS Maxillary Pilot Study)

Study name	XprESS Maxillary Pilot Study (Gould JD. 2012. *ENT J White Paper*) NCT 01525862
Objectives	To assess procedure outcomes and sinus symptom severity through 6 month follow-up after balloon sinus dilation
Location	2 US centers
Design	Prospective, multicenter, single-arm study
Duration of study	6-months
Patient population	Adults (≥18 years) with CRS of the maxillary or maxillary and ethmoid sinuses
Sample size	Not specified
Inclusion criteria	Adults (≥18 years) with uncomplicated CRS of the maxillary or maxillary and ethmoid sinuses and who had failed medical management.
Exclusion criteria	Fungal sinus disease; significant polyposis; primary ciliary dysfunction; cystic fibrosis; hemophilia; Samter's triad, sinonasal tumors; obstructive lesions; history of previous FESS; or required concomitant sinonasal surgery.
Interventions (n=) and comparators (n=)	21 participants underwent transnasal balloon dilation with the XprESS device in an office setting under local anesthesia. The baseline assessment for each participant served as the comparator.
Baseline differences	NA, each participant served as their own control.
How were participants followed-up? Duration of follow-up, lost to follow-up information	Proactive follow-up through 6 months post procedure for all participants: all 21 participants (100%) completed the 6-month follow-up.
Statistical tests	Not specified
Outcomes (including scoring methods and timing of assessments)	Short-term outcomes: Technical success Facility and procedure times Procedure tolerance Recovery outcomes Long-term outcomes (6 months): Symptom improvement (SNOT-20) Revision rate Adverse events

Table B7-8. Summary of methodology for observational studies (Eloy case series, 2012)

Study name	Eloy retrospective case series (Eloy JA, et al. 2012)
Objectives	Describe in-office experience with balloon sinus dilation in patients who failed conventional frontal sinusotomy
Location	81 US centers
Design	Retrospective, single-center case series
Duration of study	4- to 6-month follow-up
Patient population	Adult patients who had failed frontal sinusotomy
Sample size	Not specified
Inclusion criteria	Adults (≥18 years) who had failed conventional frontal sinusotomy, had symptomatically obstructed frontal sinus recess, and were treated with in-office balloon dilation of the frontal sinus recess.
Exclusion criteria	None specified
Interventions (n=) and comparators (n=)	5 participants underwent transnasal balloon dilation with the XprESS device as a standalone procedure in the frontal sinus(es). The baseline assessment for each participant served as the comparator.
Baseline differences	NA, each participant served as their own control.
How were participants followed-up? Duration of follow-up, lost to follow-up information	Retrospective chart review. Mean follow-up was 5 months (range 4-6 months).
Statistical tests	Statistical tests not performed.
Study outcomes (including scoring methods and timing of assessments)	Short-term: Technical success Procedure time Perioperative complications Long-term (4 to 6 months): Symptom improvement Frontal sinus recess patency (by endoscopy) Postoperative complications

Table B7-9. Summary of methodology for observational studies (RELIEF Study)

Study name	RELIEF (Levine SB, et al. 2013) NCT00986830
Objectives	Evaluate in-office balloon dilation of the maxillary sinus ostia and ethmoid infundibula
Location	12 US centers
Design	Prospective, multicenter, single-arm study
Duration of study	1-year
Patient population	Adults (≥18 years) with CRS
Sample size	Not specified
Inclusion criteria	Adults (≥18 years) with CRS of the maxillary sinus(es) with or without anterior ethmoid disease and according to the 2007 AAO-HNS adult sinusitis clinical practice guidelines.
Exclusion criteria	Radiological evidence of sphenoid, frontal, or posterior ethmoid disease; fungal sinus disease; polyposis, severe septal deviation, history of midface or orthognathic surgery; sinonasal surgery within 3 months; required concomitant sinonasal procedures; ciliary dyskinesia, cystic fibrosis, Samter's triad, immunosuppression; hemophilia or unable to discontinue use of anticoagulants or antiplatelet medications.
Interventions (n=) and comparators (n=)	74 participants underwent transantral balloon dilation with an XprESS equivalent device under local anesthesia in an office setting. The baseline assessment for each participant served as the comparator.
Baseline differences	NA, each participant served as their own control.
How were participants followed-up? Duration of	Proactive follow-up through 12 months post procedure. 66/69 participants (95.7%) eligible for the 12-month follow-up visit completed the visit. Five participants did not have successful

Study name	RELIEF (Levine SB, et al. 2013) NCT00986830
follow-up, lost to follow-up information	balloon dilation procedures; these participants were included in analyses for technical success, procedure tolerance, and adverse events, but excluded from the 1-year outcome analyses.
Statistical tests	2-sample t-tests (continuous variables). Nonparametric methods were used when appropriate.
Outcomes (including scoring methods and timing of assessments)	Short-term: Technical success Procedure tolerance Debridements Long-term (12 months): Symptom improvement (SNOT-20 and RSI) Healthcare utilization and work status (RSI) Revision rate Adverse events

Table B7-10. Summary of methodology for observational studies (BREATHE Study)

Study name	BREATHE (Stankiewicz J, et al. 2012, 2011; and Cutler J, et al. 2011) NCT00645762/NCT01319305
Objectives	To demonstrate the safety and long-term improvement in CRS symptoms after transantral balloon dilation of the maxillary sinus ostium and ethmoid infundibulum.
Location	11 US centers
Design	Prospective, multicenter, single-arm study
Duration of study	1 year, all participants 2 year+ data was collected under a separate protocol at 8 of the study centers (62 participants consented for this separate protocol)
Patient population	Adults (≥18 years) with CRS
Sample size	Not specified
Inclusion criteria	Adults (≥18 years) with radiological evidence of CRS of the maxillary sinus(es) or ethmoid infundibular, with or without anterior ethmoid disease, who had failed medical management.
Exclusion criteria	Radiological evidence of sphenoid, frontal, or posterior ethmoid disease; fungal sinus disease; severe septal deviation, sinonasal tumors; obstructive lesions; midfacial fractures; or polyposis.
Interventions (n=) and comparators (n=)	71 participants underwent transantral balloon dilation with an XprESS equivalent device. The baseline assessment for each participants served as the comparator. Subgroup analysis was performed on a group of participants (27%) who were treated in the office under local anesthesia.
Baseline differences	NA, each participant served as their own control.
How were participants followed-up? Duration of follow-up, lost to follow-up information	Proactive follow-up through 12 months post procedure for all participants: 67/71 participants (94.4%) completed the 12-month follow-up. Additionally, 24+ month follow-up was completed for 59/62 eligible participants (95.2%) at 8 centers that approved the long-term follow-up protocol.
Statistical tests	Paired t-tests. A repeated measures regression model was fit to compare overall SNOT-20 scores at 6 and 12 months in participants who continued in the long-term follow-up protocol with those who did not.
Outcomes (including scoring methods and timing of assessments)	Short-term outcomes: Technical success Procedure tolerance Recovery outcomes Patency (3 months) Long-term outcomes: Symptom improvement (SNOT-20 and RSI) (6, 12, and 24+ months) Healthcare utilization and work status (RSI) (12 months) Work/activity impairment (WLQ and WPAI) (12 months) Revision rate (12 and 24+ months)

Study name	BREATHE (Stankiewicz J, et al. 2012, 2011; and Cutler J, et al. 2011) NCT00645762/NCT01319305
	Satisfaction Adverse events

Table B7-11. Summary of methodology for unpublished observational studies (FinESS Registry)

Study name	FinESS Registry (Unpublished, internal data, 2011) NCT00849953
Objectives	To evaluate symptom improvement, social/emotional factors, and sinus medication use before and after balloon sinus dilation of the maxillary sinus outflow tract with or without concomitant surgery of the other sinuses and nasal anatomy.
Location	11 US centers
Design	Prospective, multicenter, single-arm registry
Duration of study	12 months
Patient population	Adults (≥18 years) with CRS of the maxillary or maxillary and ethmoid sinuses
Sample size	Not specified
Inclusion criteria	Adults (≥18 years) with uncomplicated CRS of the maxillary or maxillary and ethmoid sinuses and who were candidates for FESS.
Exclusion criteria	Excessive thickened polypoid mucosa that could inhibit transantral visualization of the maxillary sinus ostium.
Interventions (n=) and comparators (n=)	155 participants underwent transantral balloon dilation with an XprESS equivalent device. The baseline assessment for each participant served as the comparator. Subgroup analyses of balloon-only and balloon dilation with septoplasty or turbinate reductions
Baseline differences	NA, each participant served as their own control.
How were participants followed-up? Duration of follow-up, lost to follow-up information	Proactive follow-up through 12 months post procedure: 137/155 participants (88.4%) completed the 12-month follow-up.
Statistical tests	Paired t-tests. Effect size was determine for RSI symptoms.
Outcomes (including scoring methods and timing of assessments)	<u>Short-term outcomes:</u> Technical success <u>Long-term outcomes (12 months):</u> Symptom improvement (SNOT-20 and RSI) Health care utilization and work/social status (RSI) Revision rate Adverse events

Table B7-12. Summary of methodology for unpublished observational studies (Sinus Balloon Dilation in Pediatric Patients)

Study name	[redacted]
Objectives	[redacted]
Location	[redacted]
Design	[redacted]
Duration of study	[redacted]
Patient population	[redacted]
Sample size	[redacted]
Inclusion criteria	[redacted]
Exclusion criteria	[redacted]

Study name	[redacted]
	[redacted]
Interventions (n=) and comparators (n=)	[redacted]
Baseline differences	[redacted]
How were participants followed-up? Duration of follow-up, lost to follow-up information	[redacted]
Statistical tests	[redacted]
Primary outcomes (including scoring methods and timing of assessments)	[redacted]
Secondary outcomes (including scoring methods and timing of assessments)	[redacted]

7.4.2 Multiple sources of data

The REMODEL and BREATHE studies were reported in multiple publications, for final reporting, in general, outcomes are assessed at the latest time period and/or largest cohort for which they are reported.

7.4.3 Differences between patient populations and methodology in all included studies

All studies included patients with medically refractory chronic rhinosinusitis. Inclusion and exclusion criteria were very similar across studies resulting in similar overall patient populations.

Primary differences between the studies were related to the inclusion or exclusion of non-maxillary sinuses and the use of balloon devices as standalone versus hybrid procedures. REMODEL, BREATHE, RELIEF, and FinESS Registry were limited in scope to the maxillary ostia/ethmoid infundibulum with or without the presences of anterior ethmoid sinus disease while the remainder of the studies did not have such a limitation. The XprESS Registry allowed hybrid procedures.

[redacted]

7.4.4 Subgroup analyses

Subgroup analyses were performed and reported for several of the clinical studies. Whether the analyses were preplanned or post hoc is not clear in most cases. Subgroup analyses often dealt with comparisons between the following cohorts: persistent vs recurrent CRS; maxillary only vs multiple sinuses treated; and the presence or absence of anterior ethmoid disease, septal deviations, polyposis, or accessory ostia. Another frequent comparison was between balloon dilation only vs balloon dilation with concomitant sinonasal procedures. Overall, significant differences did not exist between the subgroups analyzed.

7.4.5 Accounting for participants (eligible, randomized, treated)

Table B7-13 presents the long-term follow-up accountability for the adult Entellus Medical balloon dilation studies from 6 months through 24 months, as applicable. Note that the REMODEL trial was designed to follow all participants for 12 months. After completion of the 12-month visit, participants were to complete a study visit every 6 months until the trial completion. At the time of trial completion (last enrolled participant completed their 12-month visit), a total of 66/66 (100%) and 25/25 (100%) participants completed the 18-month and 24-month visits, respectively.

Table B7-13. Participant flow for Entellus balloon dilation studies in adults

Study	Number of participants				
	Treated	6-Month	12-Month	18-Month	24-Month
REMODEL FESS	61	60	59	29	10
REMODEL Balloon Dilation	74	73	71	37	15
XprESS Multi-Sinus	81	72	76		
XprESS Registry	50[a]	46	44		
RELIEF	69	62	65		
BREATHE	71	70	67		59
FinESS Registry	155	129	137		
XprESS Maxillary Pilot	21	21			
TOTAL Balloon Dilation, followed/eligible (% follow-up compliance)	**521**	**473/521 (90.8%)**	**460/500 (92.0%)**	**37/37 (100%)**	**74/77 (96.1%)**

Grayed out cells indicate follow-up visits that were not required for the particular study.
[a] Includes only the long-term follow-up cohort from the XprESS Registry (n=50).

[redacted]

7.4.6 Rationale for participants who were lost to follow-up or withdrew from studies

As can be seen in Table B7-13, the overall follow-up compliance rate for the Entellus Medical sponsored studies has been excellent with over 90% of participants completing the required visits from 6 months through 24 months.

In the REMODEL trial, 14 FESS and 2 balloon dilation participants withdrew consent after randomization but before treatment. A majority of the participants assigned to FESS withdrew because they were unwilling to undergo the sinus surgery procedure. The trial analyses were performed on a per protocol basis and, therefore, do not include any data from the participants who withdrew before treatment.

While there was a difference in patient withdrawal between treatment groups after randomization, post-treatment dropout was extremely low; and distributed evenly between treatment groups; only 5 out of the 135 treated participants (3.7%) withdrew before the 12-month

visit (3 balloon dilation and 2 FESS participants). Both treatment arms maintained sufficient sample sizes to meet the statistical power for the primary hypotheses. Furthermore, the study eligibility criteria were very well defined to ensure evaluation of a homogenous study population of patients with rhinosinusitis. Review of the baseline characteristics of all of the patients treated confirmed that there were no significant differences in any of the baseline demographics or patient characteristics between the balloon group and the FESS group, including age, sex, ethnicity, smoking history, allergies, asthma, previous nasal surgery, septal deviation, Lund-MacKay score, CRS diagnosis, sinuses affected, duration of CRS, and SNOT-20 score.

7.5 Critical appraisal of relevant studies

Critical quality assessments for each selected study are presented in the tables below.

Table B7-14. Critical appraisal of randomized control trials (REMODEL)

Study name	**REMODEL (Chandra RK, et al. 2015; Bikhazi N, et al. 2014; Cutler J, et al. 2013) NCT01525849**	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was randomization carried out appropriately?	Yes	1:1 randomization
Was concealment of treatment allocation adequate?	Yes	Treatment assignments were placed in sequentially numbered and sealed envelopes maintained by the study sponsor. After verification of participant eligibility for the trial, the sponsor would open the seal envelope and inform the site of the treatment allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Demographics and baseline data are provided in the publications. There were no significant differences between treatment groups at baseline.
Were care providers, participants, and outcome assessors blind to treatment allocation? If not, what might be the likely impact on the risk of bias?	No to providers and participants; Yes to outcome assessors.	Blinding of the physicians and participants was not feasible due to different treatment locations and anesthesia protocols (balloon dilation done under local anesthesia in the clinic and FESS done under general anesthesia in the day theatres or main operating theatres). An independent group of blinded physicians reviewed debridement outcomes, CT scans, and data collection.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Yes	The FESS group had a higher rate of dropout between randomization and treatment. This was explained in the Cutler et al paper. No adjustments were made as a per protocol analysis was conducted.
Is there any evidence to suggest the authors measured more outcomes than they reported?	No	Between the 3 publications, all outcomes were reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	Per protocol analysis was used.

Table B7-15. Critical appraisal of observational studies (XprESS Multi-Sinus Study)

Study name	**XprESS Transnasal Maxillary Multi-Sinus Study (Gould J, et al. 2014) NCT01612780**	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Prospective enrollment. Inclusion and exclusion criteria are clearly specified.
Was the exposure accurately measured to minimize bias?	NA	The balloon dilation device is not an implantable device; exposure for each participant is limited to a brief period during the dilation procedure.
Was the outcome accurately measured to minimize bias?	Yes	Participants completed the SNOT-20 evaluation at each follow-up visit. Both objective and subjective outcomes were included.
Have the authors identified all important confounding factors?	Yes	Limitations are included in the discussion section.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Explorative and subgroup analyses. Included objective and subjective outcome measures.
Was the follow-up of patients complete?	Yes	One-year visit follow-up compliance was 94%.
How precise (in terms of confidence intervals and p values) are the results?	Yes	The results are highly significant with large effect sizes.

Table B7-16. Critical appraisal of observational studies (XprESS Registry)

Study name	**XprESS Registry (Brodner D, et al. 2013) NCT01115309**	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Prospective enrollment. Inclusion and exclusion criteria are clearly specified.
Was the exposure accurately measured to minimize bias?	NA	The balloon dilation device is not an implantable device; exposure for each participant is limited to a brief period during the dilation procedure.
Was the outcome accurately measured to minimize bias?	Yes	Safety, the primary outcome, was assessed at each visit. Both objective and subjective secondary outcomes were included.
Have the authors identified all important confounding factors?	Yes	Limitations are included in the discussion section.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Explorative and subgroup analyses. Included objective and subjective outcome measures.
Was the follow-up of patients complete?	Yes	1-month visit compliance was 98.3% (172/175) 1-year visit compliance was 88.0% (44/50)
How precise (in terms of confidence intervals and p values) are the results?	Yes	Standard deviations and p values are provided when appropriate.

Table B7-17. Critical appraisal of observational studies (XprESS Maxillary Pilot Study)

Study name	**XprESS Maxillary Pilot Study (Gould JD. 2012. *ENT J White Paper*) NCT01525862**	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an	Yes	Prospective enrollment. Inclusion and exclusion criteria

Study name	XprESS Maxillary Pilot Study (Gould JD. 2012. *ENT J White Paper*) NCT01525862	
acceptable way?		are clearly specified.
Was the exposure accurately measured to minimize bias?	NA	The balloon dilation device is not an implantable device; exposure for each participant is limited to a brief period during the dilation procedure.
Was the outcome accurately measured to minimize bias?	Yes	Participants completed the SNOT-20 evaluation at each follow-up visit. Both objective and subjective outcomes were included.
Have the authors identified all important confounding factors?	NA	As a pilot study published as a white paper, there was no discussion of confounding factors.
Have the authors taken account of the confounding factors in the design and/or analysis?	NA	Design and analysis was appropriate for a pilot study but did not discuss confounding factors.
Was the follow-up of patients complete?	Yes	6-month visit follow-up compliance was 100% (21/21)
How precise (in terms of confidence intervals and p values) are the results?	Yes	Standard deviations and p values are provided when appropriate.

Table B7-18. Critical appraisal of observational studies (Eloy retrospective case series)

Study name	Eloy retrospective case series (Eloy JA, et al. 2012)	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Retrospective chart review.
Was the exposure accurately measured to minimize bias?	NA	The balloon dilation device is not an implantable device; exposure for each participant is limited to a brief period during the dilation procedure.
Was the outcome accurately measured to minimize bias?	Not clear	The method for determining symptom improvement was not clearly defined.
Have the authors identified all important confounding factors?	NA	No statistical testing performed. This was a qualitative presentation of 1 clinic's experience.
Have the authors taken account of the confounding factors in the design and/or analysis?	NA	No statistical testing performed. This was a qualitative presentation of 1 clinic's experience.
Was the follow-up of patients complete?	Yes	Follow-up duration was not prespecified. Actual follow-up period reported.
How precise (in terms of confidence intervals and p values) are the results?	NA	No statistical testing performed. This was a qualitative presentation of 1 clinic's experience.

Table B7-19. Critical appraisal of observational studies (RELIEF Study)

Study name	RELIEF (Levine SB, et al. 2013) NCT00986830	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Prospective enrollment. Inclusion and exclusion criteria are clearly specified.
Was the exposure accurately measured to minimize bias?	NA	The balloon dilation device is not an implantable device; exposure for each participant is limited to a brief period during the dilation procedure.
Was the outcome accurately measured to minimize bias?	Yes	Participants completed the SNOT-20 evaluation at each follow-up visit. Both objective and subjective outcomes were included.

Study name	RELIEF (Levine SB, et al. 2013) NCT00986830	
Have the authors identified all important confounding factors?	Yes	Limitations are included in the discussion section.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Explorative and subgroup analyses. Included objective and subjective outcome measures.
Was the follow-up of patients complete?	Yes	1-year visit compliance was 95.7% (66/69 treated subjects)
How precise (in terms of confidence intervals and p values) are the results?	Yes	Standard deviations and p values are provided when appropriate.

Table B7-20. Critical appraisal of observational studies (BREATHE Study)

Study name	BREATHE (Stankiewicz J, et al. 2012, 2011; and Cutler J, et al. 2012) NCT00645762/NCT01319305	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Prospective enrollment. Inclusion and exclusion criteria are clearly specified.
Was the exposure accurately measured to minimize bias?	NA	The balloon dilation device is not an implantable device; exposure for each participant is limited to a brief period during the dilation procedure.
Was the outcome accurately measured to minimize bias?	Yes	Participants completed the SNOT-20 evaluation at each follow-up visit. Both objective and subjective outcomes were included.
Have the authors identified all important confounding factors?	Yes	Limitations are included in the discussion section.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Explorative and subgroup analyses. Included objective and subjective outcome measures.
Was the follow-up of patients complete?	Yes	1-year visit follow-up compliance was 94% (67/71) 2-year visit compliance was 95% (59/62)
How precise (in terms of confidence intervals and p values) are the results?	Yes	Standard deviations and p values are provided when appropriate.

Table B7-21. Critical appraisal of observational studies (FinESS Registry)

Study name	FinESS Registry (Unpublished, internal data, 2011) NCT00849953	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Prospective enrollment. Inclusion and exclusion criteria are clearly specified.
Was the exposure accurately measured to minimize bias?	NA	The balloon dilation device is not an implantable device; exposure for each participant is limited to a brief period during the dilation procedure.
Was the outcome accurately measured to minimize bias?	Yes	The preferred method of collection of the SNOT-20 and RSI assessments at follow-up was by mail to avoid potential bias by patient interaction with investigators.
Have the authors identified all important confounding factors?	NA	The study was not published; therefore, no discussion of limitations is available.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Two-thirds of participants were treated with standalone balloon dilation and analyzed as a separate subgroup.
Was the follow-up of patients	Yes	1-year visit follow-up compliance was 88.4% (137/155)

Study name	FinESS Registry (Unpublished, internal data, 2011) NCT00849953	
complete?		
How precise (in terms of confidence intervals and p values) are the results?	Yes	Standard deviations, effect sizes, and p values are provided when appropriate.

Table B7-22. Critical appraisal of observational studies (Sinus Balloon Dilation in Pediatric Patients)

Study name	Sinus Balloon Dilation in Pediatric Patients (Publication expected in 2016) NCT02278484	
Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	[redacted]	[redacted]
Was the exposure accurately measured to minimize bias?	[redacted]	[redacted]
Was the outcome accurately measured to minimize bias?	[redacted]	[redacted]
Have the authors identified all important confounding factors?	[redacted]	[redacted]
Have the authors taken account of the confounding factors in the design and/or analysis?	[redacted]	[redacted]
Was the follow-up of patients complete?	[redacted]	[redacted]
How precise (in terms of confidence intervals and p values) are the results?	[redacted]	[redacted]

7.6 Results of relevant studies

Results for each of the selected published and unpublished studies are presented in the tables below.

Table B7-23. REMODEL randomized controlled trial published results

Overall outcomes	Balloon Dilation, N=74 Mean or %	FESS (control), N=61 Mean or %	P value[a]	Conclusion
Primary efficacy endpoints				
One-year change in SNOT-20	–1.59	–1.60	<0.0001	Balloon dilation is noninferior to FESS
Debridements per subject (n)	0.2	1.0	<0.0001	Balloon dilation is superior to FESS
Secondary efficacy outcomes (recovery, short-term, and procedure)				
Technical success	99.3%	99.4%	NS	No significant difference between trial arms
Subjects discharged with nasal bleeding	32%	56%	0.009	Balloon dilation is significantly better than FESS
Recovery time (days)	1.7	5.0	<0.0001	Balloon dilation is significantly better than FESS
Duration of prescription pain medications (days)	1.0	2.8	<0.0001	Balloon dilation is significantly better than FESS
Duration of over-the-counter pain medications (days)	1.8	2.6	NS	No significant difference between trial arms
Postoperative nausea	9.5%	11.5%	NS	No significant difference between trial arms
Short-term change in SNOT-20 (1 week/1 month)	–1.32/–1.56	–0.94/–1.53	NS	No significant difference between trial arms
Secondary efficacy outcomes (1 year)				
Change in number of rhinosinusitis episodes per subject	–4.2	–3.7	NS	No significant difference between trial arms
Ostial patency	91.9% (124/135)	97.4% (111/114)	NS	No significant difference between trial arms
Mean reduction of activity impairment due to CRS	68%	76%	NS	No significant difference between trial arms
Mean reduction in overall work impairment due CRS	72%	80%	NS	No significant difference between trial arms
Mean reduction in productivity loss	74%	78%	NS	No significant difference between trial arms
Revision surgery rate (1-year)	1.4% (1/71)	1.7% (1/59)	NS	No significant difference between trial arms
Subject satisfaction	90.1% (64/71)	94.8% (55/58)	NS	No significant difference between trial arms
Safety outcomes				
Complication rate	0% (0/74)	0% (0/61)	NS	No significant difference between trial arms

Results are presented as % (n/N) or mean. Abbreviations: CRS, chronic rhinosinusitis; FESS, functional endoscopic sinus surgery; NS, not significant; SNOT-20, 20-item Sino-Nasal Outcome Test.

[a] Comparison of difference between study arms.

Table B7-24. XprESS Multi-Sinus Study published results

Overall outcomes	Result	P value[a]	Conclusion/Comments
Primary efficacy endpoint			
One-year change in SNOT-20	–1.57	<0.0001	Statistically significant and clinically meaningful change
Secondary efficacy outcomes (short-term)			
Technical success (sinuses)	98.1% (307/313)	NA	

Overall outcomes	Result	P value[a]	Conclusion/Comments
Procedure tolerance	2.8 ± 2.2	NA	Scores range from 0 (no pain) to 10 (severe pain)
Secondary efficacy outcomes (1 year)			
RSI major symptoms	–1.5 to –2.5	<0.0001	Comparing 12 months before with 12 months after procedure. Large effect sizes (–0.99 to –1.61)
Proportion using steroids	–22.6%	<0.001	Comparing 12 months before with 12 months after procedure
Proportion using antihistamines	–22.7%	<0.0001	
Antibiotic courses	–2.4	<0.0001	
Work/school days missed	–0.7	0.037	
Homebound days	–5.2	<0.0001	
Sinus-related physician visits	–3.0	<0.0001	Comparing 12 months before with 12 months after procedure
Acute sinus infections	–2.3	<0.0001	
Revision surgery rate (1-year)	1.3% (1/82)	NA	
Subject satisfaction	87.8% (65/74)	NA	
Safety outcomes			
Serious device or procedure-related adverse events	0% (0/82)	NA	

Results are presented as % (n/N) or mean. Abbreviations: NA, not applicable; RSI, Rhinosinusitis Symptom Inventory; SNOT-20, 20-item Sino-Nasal Outcome Test.

[a] Paired *t*-test for mean change from baseline.

Table B7-25. XprESS Registry published results

Overall outcomes	Result	P value[a]	Conclusion/Comments
Short-term outcomes (procedure through 3 months, N=175)			
Technical success (sinuses)	96.4% (479/497)	NA	
Long-term outcomes (1 year, N=44)			
Change in SNOT-20 score	–1.1	<0.0001	Statistically significant and clinically meaningful change
Patency (per sinus)	91.6% (76/83)	NA	
Proportion using steroids	–21.1%	0.007[b]	Comparing 12 months before with 12 months after procedure
Antibiotic courses	–2.0	0.0001	
Work/school days missed	–12.1	0.02	
Sinus-related physician visits	–1.7	0.03	
Acute sinus infections	–2.6	NS	
Revision surgery rate (1-year)	2.3% (1/44)	NA	
Safety outcomes			
Serious adverse events	0% (0/175)	NA	

Results are presented as % (n/N) or mean. Abbreviations: NA, not applicable; NS, not statistically significant; SNOT-20, 20-item Sino-Nasal Outcome Test.

[a] Paired *t*-test for mean change from baseline.

[b] McNemer's test.

Table B7-26. XprESS Maxillary Pilot results published in *ENT Journal* White Paper

Overall outcomes	Result	P value[a]	Conclusion/Comments
Short-term outcomes			
Technical success (sinuses)	100% (42/42)	NA	
Procedure tolerance	1.8 ± 1.8	NA	Scores range from 0 (no pain) to 10 (severe pain)
Proportion using Rx or OTC	28.6% (6/21)	NA	

Overall outcomes	Result	P value[a]	Conclusion/Comments
pain medication			
Duration of OTC pain medication use (days)	1.9	NA	In participants using OTC pain medication.
Duration of Rx pain medication use (days)	1.2	NA	In participants using Rx pain medication.
Recovery time (days)	0.67 ± 0.74	NA	
Long-term outcomes (6 months)			
Change in SNOT-20 score	–1.5	<0.0001	Statistically significant and clinically meaningful change.
Revision surgery rate	0% (0/21)	NA	
Satisfaction	95% (20/21)	NA	
Safety outcomes			
Serious adverse events	0% (1/21)	NA	Unrelated to balloon device or procedure.

Results are presented as % (n/N) or mean (±SD). Abbreviations: NA, not applicable; OTC, over-the-counter; Rx, prescription; SNOT-20, 20-item Sino-Nasal Outcome Test.

[a] Paired *t*-test for mean change from baseline.

Table B7-27. Eloy retrospective case series published results

Overall outcomes	Result	P value[a]	Conclusion/Comments
Short-term outcomes			
Technical success (sinuses)	100% (5/5)	NA	
Long-term outcomes (5 months)			
Symptom improvement	100% (5/5)	NA	Asymptomatic post procedure (method not specified)
Patency (per participant)	100% (5/5)	NA	Number of sinuses not specified
Safety outcomes			
Complications	0% (0/5)	NA	

Results are presented as % (n/N) or mean [range]. Abbreviations: NA, not applicable.

Table B7-28. RELIEF Study published results

Overall outcomes	Result	P value[a]	Conclusion/Comments
Short-term outcomes			
Technical success (sinuses)	91.9% (124/135)	NA	
Procedure tolerance	3.2	NA	Scores range from 0 (no pain) to 10 (severe pain)
Debridements	0% (0/74)	NA	
Long-term outcomes (1 year)			
Change in SNOT-20 score	–1.2	<0.0001	Statistically significant and clinically meaningful change
RSI major symptoms	–1.1 to –2.0	<0.01	Comparing 12 months before with 12 months after procedure. Large effect sizes (–0.81 to –1.29) for all major symptoms except rhinorrhea (–0.49, small, *p*=0.07) in the recurrent acute subgroup.
Proportion using steroids	–16.3%/18.7%	0.036/NS	Comparing 12 months before with 12 months after procedure (persistent CRS/recurrent acute rhinosinusitis)
Proportion using antihistamines	–4.1%/18.7%	NS/NS	

Overall outcomes	Result	P value[a]	Conclusion/Comments
Antibiotic courses	–3.0/–3.8	<0.0001/0.001	
Work/school days missed	–6.2/–5.1	<0.0001/0.061	
Homebound days	–6.8/–4.5	0.024/0.047	
Sinus-related physician visits	–4.7/–4.7	<0.0001/<0.0001	
Acute sinus infections	–3.4/–4.4	<0.0001/<0.001	
Revision surgery rate	5.8% (4/69)	NA	
Safety outcomes			
Serious adverse events	1.4% (1/74)	NA	Unrelated to balloon device or procedure

Results are presented as % (n/N) or mean. Abbreviations: CRS, chronic rhinosinusitis; NA, not applicable; NS, not statistically significant; RSI, Rhinosinusitis Symptoms Inventory; SNOT-20, 20-item Sino-Nasal Outcome Test.

[a] Paired *t*-test for mean change from baseline.

Table B7-29. BREATHE Study published results

Overall outcomes	Result	P value[a]	Conclusion/Comments
Short-term outcomes			
Technical success (sinuses)	97.7% (129/132)	NA	
Debridements (per participant)	0.03	NA	Reported in the discussion section of 2-year publication
Procedure tolerance	2.5	NA	Scores range from 0 (no pain) to 10 (severe pain). Includes in-office participants (19), patients under local only in the operating theatre (8), and patients under local + IV sedation in the operating theatre (33).
Recovery time	88% within 2 days	NA	Mean value not provided.
Patency (per sinus at 3 mo.)	90.6% (106/117)	NA	Accessed by CT scan.
Long-term outcomes (1 year)			
Change in SNOT-20 score	–1.8	<0.0001	Statistically significant and clinically meaningful change
Revision surgery rate	4.2% (3/71)	NA	
Satisfaction	89% (59/66)	NA	
Reduction in work productivity loss (WLQ)	73%	<0.0001	
Reduction in work productivity loss (WPAI)	76%	<0.0001	
Long-term outcomes (2 year)			
Change in SNOT-20 score	–1.86	<0.0001	Statistically significant and clinically meaningful change
Revision surgery rate	6.8% (4/59)	NA	
Satisfaction	91.5% (54/59)	NA	
Safety outcomes			
Serious adverse events	4.2% (3/71)	NA	Only 1 event was related to the balloon device or procedure (subcutaneous emphysema)

Results are presented as % (n/N) or mean. Abbreviations: NA, not applicable; SNOT-20, 20-item Sino-Nasal Outcome Test; WLQ, Work Limitations Questionnaire; WPAI, Work Productivity and Activity Impairment questionnaire.

[a] Paired *t*-test for mean change from baseline.

Table B7-30. FinESS Registry unpublished results

Overall outcomes	Result	P value[a]	Conclusion/Comments
Short-term outcomes			
Technical success (sinuses)	95% (288/302)	NA	

Overall outcomes	Result	P value[a]	Conclusion/Comments
Work/school days missed	–2.8	<0.0001	
Homebound days	–5.1	<0.0001	
Sinus-related physician visits	–3.9	<0.0001	
Acute infections	–6.0	0.025	
Long-term outcomes (1 year)			
Change in SNOT-20 score	–1.2	<0.0001	Statistically significant and clinically meaningful change.
Change in major RSI symptoms	–1.3 to –2.0	<0.0001	Comparing 12 months before with 12 months after procedure.
Revision surgery rate	3.0% (4/135)	NA	
Safety outcomes			
Serious adverse events	0% (1/155)	NA	Unrelated to balloon device or procedure.

Results are presented as % (n/N) or mean. Abbreviations: NA, not applicable; RSI, Rhinosinusitis Symptom Inventory; SNOT-20, 20-item Sino-Nasal Outcome Test.

[a] Paired *t*-test for mean change from baseline.

Table B7-31. Sinus Balloon Dilation in Pediatric Patients unpublished results

Overall outcomes	Result	P value[a]	Conclusion/Comments
Primary outcomes			
Technical success (sinuses)	[redacted]	[redacted]	
Complication rate	[redacted]	[redacted]	
Long-term outcomes (6 month)			
Change in SN-5 score	[redacted]	[redacted]	[redacted]
Change in SNOT-22 score	[redacted]	[redacted]	[redacted]
Change in major RSI symptoms	[redacted]	[redacted]	[redacted]
Revision surgery rate	[redacted]	[redacted]	

Results are presented as % (n/N) or mean. Abbreviations: NA, not applicable; RSI, Rhinosinusitis Symptom Inventory; SN-5, Sinus and Nasal Quality of Life Survey; SNOT-20, 20-item Sino-Nasal Outcome Test.

[a] Paired *t*-test for mean change from baseline.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Identification of studies on adverse events

All of the articles selected and summarized in section 7.3 assessed complications or adverse events as a study outcome. None of the studies were statistically powered for the detection of

safety event rates. The reporting of adverse events varied across studies with some reporting all serious and non-serious events while others reported only device- and procedure-related adverse events. Despite this variability in reporting, it is clear that serious adverse events related to the balloon device or procedure are very rare.

7.7.2 Details of important adverse events reported in selected studies

Of the over 500 adult study participants treated in the Entellus Medical sponsored studies, there has been only 1 potentially serious device- or procedure-related adverse event (<0.2%). In the BREATHE study, 1 subject experienced subcutaneous emphysema (facial swelling) after resuming continuous positive airway pressure (CPAP) the same evening as the procedure. The event resolved spontaneously within 1 week.[Cutler, et al. 2011] A warning was added to the XprESS Instructions for Use (IFU) to not use CPAP until the physician has confirmed that the tissue has adequately healed.

In the full body of literature on balloon sinus dilation (any manufacturer), there are only a small number of rare serious device- or procedure-related adverse events reported: subcutaneous emphysema (1), orbital wall fracture (1), CSF leak (1), and cardiac arrest from vasovagal stimulation possibly due to orbital wall damage (1).

For comparison, complication rates during endoscopic sinus surgery utilizing rigid tools have been reported to be approximately 1%. [Ramakrishnan et al. 2012; May and Levine. 2004; Rombout and de Vries. 2001] Complications associated with FESS include vascular injury, intracranial injury (including CSF leak), orbital injury (including blindness), and olfactory deficits.

7.7.3 Adverse events and outcomes from national regulatory databases

In the XprESS postmarket experience (surveillance) from February 2010 through December 2015, 7 CSF leaks and 1 case of orbital wall damage have occurred and been reported in the FDA MAUDE database. These reports include cases of standalone balloon dilation and hybrid procedures (balloon dilation combined with FESS).

7.7.4 Overview of safety of technology

Complication rates for balloon dilation are very low (<0.2%) as compared to an estimate for FESS of 1%. Balloon dilation procedures have been performed in main operating theaters, day theatres, and in physician offices as both standalone and hybrid procedures. These results demonstrate that balloon dilation is safe when performed in any of these settings.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

A meta-analysis of participant-level data from the standalone balloon dilation studies using the Entellus Medical devices was recently reported by Chandra, et al.[*Laryngoscope,* 2016] This

meta-analysis included data from 6 of the 7 Entellus Medical-sponsored studies listed in Section 7.3. Because the focus of the meta-analysis was on standalone balloon sinus dilation, the XprESS Registry was not included in the meta-analysis due to the large proportion of the participants who underwent concomitant sinonasal procedures with the balloon dilation (hybrid procedures).

7.8.1 Meta-analysis methodology

Participant-level data from the 358 participants (846 sinuses) were compiled for meta-analysis and analyzed by an independent biostatistician. The 6 studies included in the meta-analysis were: REMODEL balloon dilation arm, XprESS Multi-Sinus Study, XprESS Maxillary Pilot Study, RELIEF Study, FinESS Registry, and BREATHE. Since all the studies except REMODEL were single-arm studies, the primary comparator for the meta-analysis was the change from baseline values. The REMODEL FESS arm was used as an additional comparator for selected outcomes. Statistical significance for the change from baseline was assessed using paired *t*-tests. Comparisons between the REMODEL balloon dilation arm, REMODEL FESS arm, and the 5 pooled single-arm studies were assessed using analysis of variance *F* tests (continuous variables) and Chi-square tests (categorical variables). To estimate population means and changes from baseline for continuous outcomes, random effects models were used with linear mixed models estimated by the restricted likelihood method. The random effects models accounted for repeated measures within participant and between study variances.

Participant numbers and compliance with study visits are shown in Table B7-13. Participant follow-up was consistently very high across studies and >90% at 6-, 12-, 18-, and 24-month visits, as applicable.

Outcomes were defined consistently across studies. Technical success and SNOT-20 scores were reported for all 6 studies. The other outcomes were reported in anywhere from 2 to 5 studies with sample sizes per outcome ranging from 74 to 355 participants.

7.8.2 Evidence synthesis

Comparison of demographics and baseline characteristics demonstrated no statistically significant differences across the 6 standalone balloon dilation studies. Table B7-32 presents the short-term outcomes from the meta-analysis.

Table B7-32. Meta-analysis results of short-term outcomes

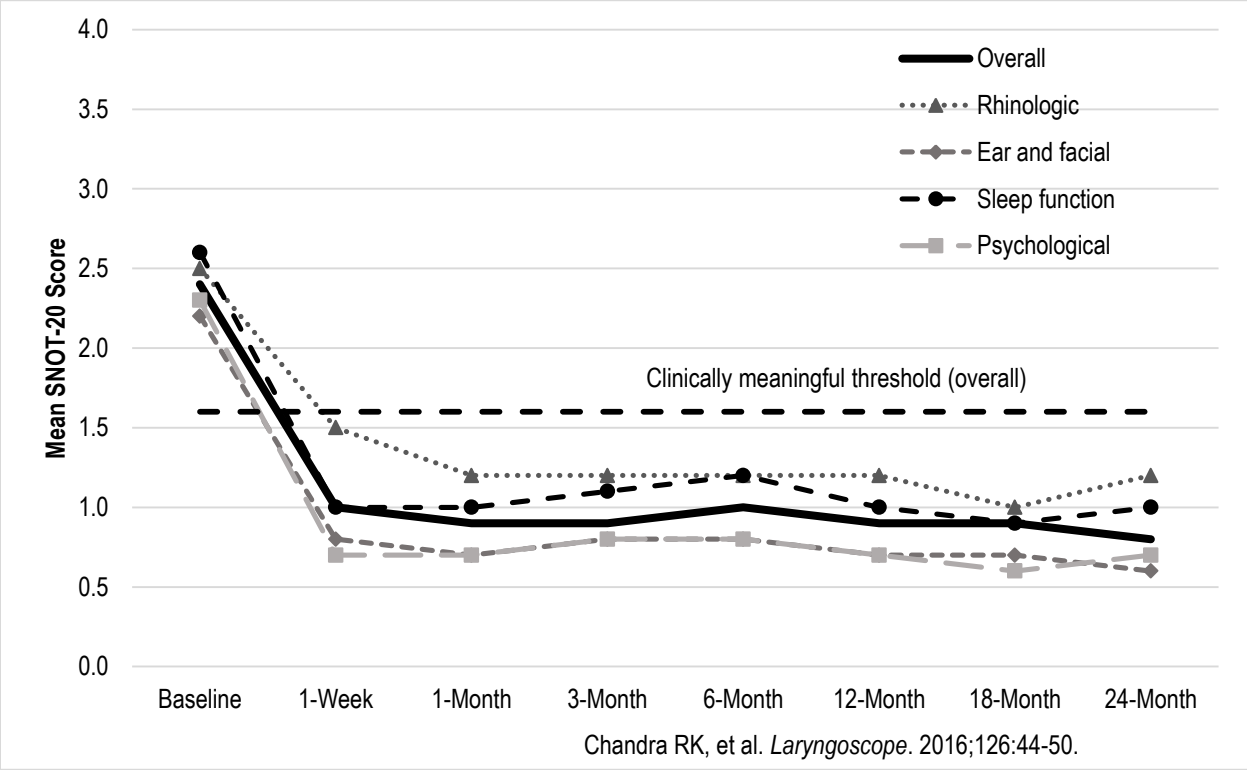
Overall outcomes	N	Result
Technical success (sinuses)	846	97.5% (825)
Debridements per participant	145	0.16 ± 0.55
Recovery time (days)	94	1.4 ± 1.3
Procedure tolerance[a]	241	2.6 ± 2.3
Postoperative nausea	166	12.7% (21)
Postoperative nasal bleeding	232	13.8% (32)
Duration of Rx pain medication use (days)	94	0.8 ± 1.3
Duration of OTC pain medication use (days)	94	1.5± 2.7

Results are presented as mean ± standard deviation or % (n). Abbreviations: OTC, over-the-counter; Rx, prescription. From Chandra RK, et al. *Laryngoscope*. 2016;126:44-50.

[a] Scores range from 0 (no pain) to 10 (severe pain).

The meta-analysis demonstrated statistically significant and clinically meaningful (≥0.8) improvements in sinus symptoms at 12 and 24 months after balloon dilation in populations of 310 and 74 patients, respectively. The meta-analysis change from baseline in the SNOT-20 symptom scores at 12 months and 24 months were -1.5 and -1.8 ($p<0.0001$ compared to baseline). The results of the random effects model on the overall and subscale SNOT-20 scores are shown in Figure B7-2. The change in SNOT-20 scores were statistically significant, clinically meaningful, and durable through 24 months. A further comparison demonstrated no statistically significant differences between the SNOT-20 results from the FESS arm and the balloon arm of the REMODEL trial and the 5 pooled single-arm studies.

Figure B7-2. Meta-analysis random effects model for SNOT-20 overall and subscale scores



There were no statistical differences in the 12-month revision rates between the FESS arm of the REMODEL trial (1.7%), the balloon arm of the REMODEL trial (1.4%), and the 5 pooled single-arm balloon dilation studies (3.2%, p=0.628).

The meta-analysis results of the change from baseline for the RSI scores for health care use and work/social status are presented in Table B7-33. There were statistically significant changes from baseline in both health care use and work/social measures.

Table B7-33. Meta-analysis of standalone balloon dilation studies: changes in RSI health care use and work status from baseline to 12 months

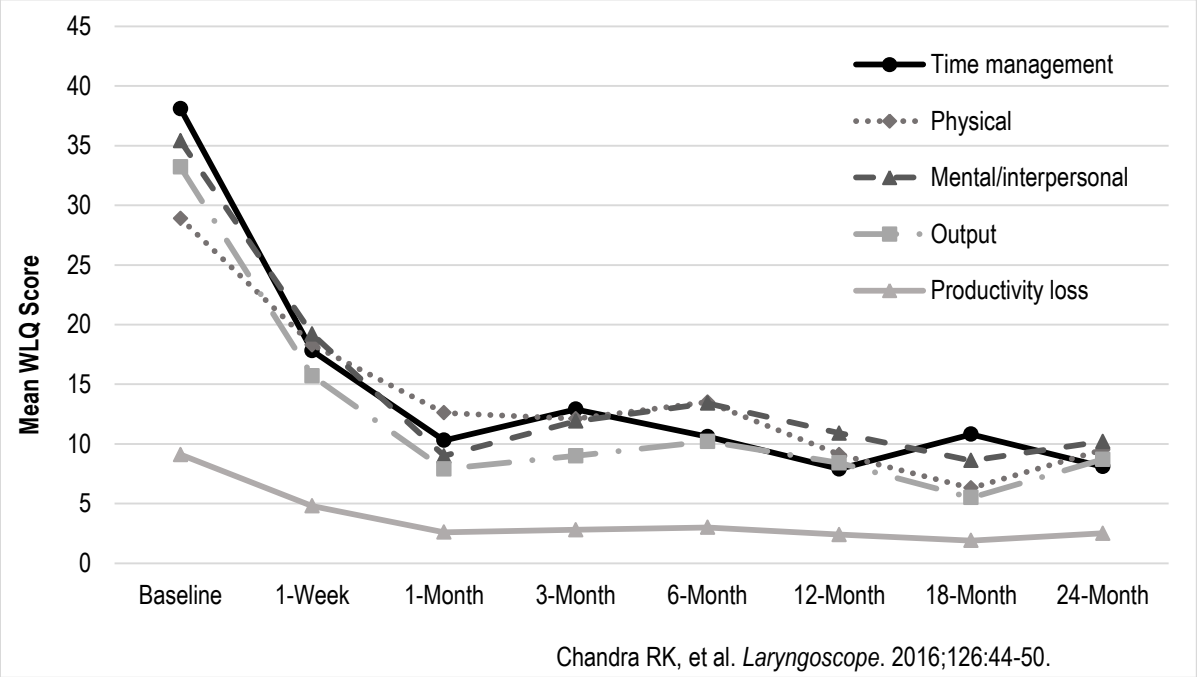
RSI Parameter	N	Baseline[a]	12-Month[a]	Change[a]	P value[b]
Work/school missed due to nasal problems (days)	161	8.5 ± 11.0	3.6 ± 5.9	-5.0 ± 9.5	<0.0001

RSI Parameter	N	Baseline[a]	12-Month[a]	Change[a]	P value[b]
Homebound due to nasal problems (days)	167	8.3 ± 14.4	2.0 ± 6.5	-6.3 ± 11.3	<0.0001
Number of physician/nurse visits for nasal problems	172	6.8 ± 10.6	2.3 ± 7.0	-4.5 ± 11.5	<0.0001
Number of acute infections of nose/sinuses	167	5.4 ± 4.8	1.5 ± 2.4	-3.9 ± 4.5	<0.0001
Number of antibiotic courses	165	4.5 ± 2.9	1.6 ± 2.1	-2.9 ± 3.1	<0.0001

[a] Data displayed as Mean ± SD. From Chandra RK, et al. *Laryngoscope*. 2016;126:44-50.
[b] Comparison of mean change from baseline to follow-up; *p* value from paired *t*-test.

Employed participants of the REMODEL and BREATHE studies completed the Work Limitation Questionnaire (WLQ) through 24 months post procedure. A random effects model demonstrated statistically significant improvements from baseline for 4 of the 5 measured domains (time management, mental/interpersonal, outcome, and productivity loss). The random effects output is displayed in Figure B7-3.

Figure B7-3. Meta-analysis random effects model for WLQ over time



7.9 Interpretation of clinical evidence

7.9.1 Statement of principal findings

Published clinical literature, medical society endorsements, and wide acceptance by practicing physicians support the use of standalone or hybrid balloon dilation for the treatment of CRS. The Entellus Medical balloon sinus dilation devices, specifically, have been studied in well-designed studies, including 1 patient-level meta-analysis; 1 statistically powered, prospective, multicenter RCT; 7 prospective, multicenter, single-arm studies; and 1 retrospective, single-center, single-arm study. The clinical evidence from many of these studies has been published in 10 peer-reviewed articles and 1 white paper. The studies consistently included clinically relevant

outcomes. Multiple studies provide consistent data documenting that balloon dilation is safe and results in significant, sustained sinus symptom improvement, low debridement rate, high patency, quick recovery, a low surgical revision rate, and improved health care utilization. These data demonstrate that the health benefits of balloon dilation outweigh the risks. Most significantly, the patient-level meta-analysis and the long-term results from the larger cohort of the REMODEL RCT [Chandra et al, 2016] demonstrate that balloon dilation improves the net health outcome and is as beneficial as the established alternative of FESS for a wide range of endpoints.

Based on the information provided, sinus balloon dilation should be considered medically necessary as a covered payable procedure for patients with uncomplicated CRS when medical management has failed.

7.9.2 Summary of the strengths and limitations

The clinical evidence provided in this report includes data on over 500 participants (over 1500 sinuses) treated in 9 clinical studies with follow-up of up to 24 months post procedure. Most notably, in addition to a number of prospective, multicenter, single-arm studies, this evidence includes the only statistically powered randomized controlled trial comparing balloon sinus dilation to FESS that has been published to date. Each of the studies used well defined inclusion and exclusion criteria that aligned with the AAO-HNSF and EPOS 2007 guidelines including failure to respond to medical management. The follow-up compliance for each of the studies was excellent with a mean follow-up compliance of >90%. Outcomes included clinically relevant measures with both subjective and objective assessments. Repeated measures of validated patient-reported outcomes over extended time periods reduced potential bias. The results were remarkably consistent for all outcomes across the studies.

Additional strengths of specific studies include analysis of important clinical subgroups in a number of studies. The inclusion of clinically important subgroups such as patients with ethmoid sinus disease and septal deviations facilitates generalisation of the study results to clinical practice.

The selected studies include limitations that deserve mention. Although the REMODEL trial was randomized, the participants and investigators were not blinded to the treatment assignment. Blinding of the trial was not feasible since the balloon dilation participants were treated in the physician’s office under local anesthesia while the FESS participants were typically treated in a surgical setting under general anesthesia. Moreover, postoperative endoscopies and CT scans would have made the treatment assignment apparent to the treating physicians. To address the unblinded trial design and reduce bias, 2 independent (blinded) physicians reviewed and verified primary endpoint documentation.

Several of the studies also limited balloon sinus dilation to the maxillary ostia/ethmoid infundibula. In most cases, this was because the indication for the FinESS device was only for the maxillary ostia/ethmoid infundibula. For the REMODEL trial that included use of the both the XprESS and FinESS devices, the trial was designed for treatment limited to the maxillary ostia/ethmoid infundibular due to statistical considerations. However, the results of the XprESS

Multi-Sinus Study demonstrate that participants experience similar sinus symptom improvement after balloon dilation regardless of which sinuses are treated.

Another limitation is that a few of the studies allowed concomitant sinonasal procedures including FESS for sinuses not treated with balloon dilation. Although this theoretically confounds the ability to determine which procedure contributed to the participant's improvement, the results of these studies are very consistent with the outcomes seen in the studies that did not permit concomitant procedures. Particularly, the REMODEL randomized controlled trial did not permit concomitant procedures and demonstrated noninferiority of balloon dilation with FESS with regard to symptom improvement and superiority with regard to postoperative debridements.

7.9.3 Relevance of the evidence base to the scope

The clinical evidence provided in this report is directly relevant to the scope of this application. The clinical evidence presented includes results from all of the published and unpublished clinical studies relevant to the XprESS device for the treatment of chronic rhinosinusitis. The evidence includes a randomized controlled trial and meta-analysis in addition to a number of multicenter, prospective, single-arm studies. The randomized controlled trial provides a direct comparison of balloon sinus dilation with the standard of care treatment, FESS. Objective and subjective clinical outcomes from all the studies are presented, including technical success, disease-specific quality of life improvements, postoperative debridement requirements, revision surgery, recovery time, ostial patency, nasal bleeding, procedure pain, postprocedure medication use, and work/school productivity. Study results include treatment of maxillary, frontal and sphenoid sinuses. Additionally, the clinical evidence includes analyses of outcomes for patients in the following subgroups: chronic vs recurrent acute rhinosinusitis, with or without nasal polyps, with or without anterior ethmoid sinus disease, with or without septal deviations, with or without accessory ostia, and in children as young as 2 years old.

7.9.4 Factors that may influence external validity of study results to routine clinical practice

The clinical study results are expected to translate directly to routine clinical practice based on the inclusion of patient populations who met standard criteria for FESS after failing medical management for their CRS symptoms. The balloon dilation studies have used the devices according to cleared indications for use and the manufacturer's IFUs. The consistency and durability of the data across a number of studies suggests that the same benefits should be attainable in routine clinical practice.

7.9.5 Patient selection criteria

The appropriate patients for balloon sinus dilation treatment can be identified by extrapolating the investigational study patient selection criteria to the usual conditions for medical practice.

The patient eligibility criteria for the balloon clinical studies were well-defined and explicitly stated in the "Methods" section of each study publication. Inclusion criteria were similar across studies with most of the studies using the definition of CRS as laid out by the AAO Clinical Practice Guideline [Rosenfeld et al, 2007] or the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [Fokkens et al, 2012]. Exclusion criteria were also similar and generally excluded patients with ciliary dysfunction, cystic fibrosis, sinonasal tumors or obstructive

lesions, history of facial trauma; severe/gross polypoid disease, Samter's triad, and severe sinus fungal disease. The meta-analysis by Chandra, et al. further demonstrated no significant differences in demographic or baseline characteristics between the studies, confirming similar patient populations.

Based on the similarity in patient inclusion and exclusion criteria for balloon dilation studies, and based on the consistency of the positive outcomes achieved between studies, there is sufficient evidence to demonstrate that health improvement is attainable outside the investigational setting for *patients with uncomplicated CRS who meet the criteria for medically necessary FESS*.

Based on the clinical evidence to date, there is insufficient evidence to demonstrate that health improvement is attainable outside the investigational setting for patients with the following complications or diseases; therefore, these patients may not be good candidates for standalone balloon dilation and may require conventional sinus surgery:

- Ciliary dysfunction
- Cystic fibrosis
- Sinonasal tumors or obstructive lesions
- History of facial trauma
- Severe/gross polypoid disease
- Severe fungal sinusitis

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Section C – Economic evidence

Section C will be provided as a separate document within the NICE timelines.

Attachments

The following attachments are provided in a separate document.

Attachment 1: XprESS Multi-Sinus Dilation System Instructions for Use

Attachment 2: XprESS Multi-Sinus Dilation System CE mark certificate

Attachment 3: Quality systems (ISO 13485) certificate

Attachment 4: Bibliography and PDF copies of selected articles

Attachment 5: Structured abstracts of unpublished studies

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence: MT288

Evaluation title: The XprESS Multi-Sinus Dilation System for the treatment of chronic rhinosinusitis

Sponsor: Entellus Medical, Inc.

Date sections A and B submitted: A and B submitted: February 15, 2016

Date section C submitted: Submitted March 8, 2016 separately

Table of Contents

Glossary of terms

Term	Definition
BCD:	Balloon Catheter Device
CCA:	Cost Consequence Analysis
CRS:	Chronic Rhinosinusitis
FESS:	Functional Endoscopic Sinus Surgery
HES:	Hospital Episode Statistics
HRQoL:	Health Related Quality of Life
MSDS:	Multi-Sinus Dilation System
NHIS:	National Health Interview Survey
NHS:	National Health Service

NICE: National Institute for Health and Care Excellence
RR: Relative Risk
RCT: Randomised Controlled Trial
SLR: Systematic Literature Review
TP: Transition Probability

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Published studies

A systematic literature search was conducted using the following databases and parameters:

Databases Searched: Medline (via OVID), Medline (via Pubmed), Embase (via OVID), Cochrane Database of Systematic Reviews (via Wiley), NHS EED* (via University of York, Center for Reviews & Dissemination (CRD) website).
* NIHR funding to produce DARE and NHS EED ceased at the end of March 2015. However, both databases can still be accessed via the CRD website. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014. Bibliographic records were published on DARE and NHS EED until 31st March 2015. The HTA database will continue to

be produced by CRD for the foreseeable future.

Date of Search: February 22, 2016

Search date span: 2010 to February 22, 2016

Similar search of the literature was conducted, as in section B of the clinical evidence with additional search terms to fully identify the relevant cost economic evaluation studies. Terms included were: models, economic, costs and cost analysis, economics, insurance, model or models or modelling, cost or costs or cost-analysis, claim or claims or charge.

8.1.1 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature.

Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients with chronic rhinosinusitis
Interventions	Balloon sinus dilation using the XprESS Multi-Sinus Dilation System or equivalent. Functional endoscopic sinus surgery (FESS) (comparator intervention)
Outcomes	Costs, incremental costs, net budget impact or cost-effectiveness, including cost per Quality Adjusted Life Year (QALY)
Study design	Full economic evaluations (including technology appraisals) of XprESS or equivalent and FESS procedure, partial economic evaluations, cost-effectiveness analysis alongside trial, economic modelling studies, costing studies (including insurance claims data bases and budget impact models), incidental cost-effectiveness analysis, Clinical Trials, Case Reports, Technology Assessments and Meta-analyses/Reviews
Language restrictions	English
Search dates	2010 to February 22, 2016
Exclusion criteria	
Population	Patients with conditions other than chronic rhinosinusitis, cadaver studies, non-human studies
Interventions	Sinus surgery procedures not involving balloon technology or FESS
Outcomes	Only presents data on the clinical effectiveness (meta-analysis, RCT, clinical study),inability to

	differentiate the costs associated with XprESS, FESS or comparator balloon sinus dilation procedure
Study design	Medical policy statements, reviews, letter to the editors, clearly commentary only with no data from primary studies. Clearly narrative review (no mention of any database searched). Conference abstract 2009 or older.
Language restrictions	Non-English
Search dates	Before 2010

8.1.2 Report the numbers of published studies included and excluded at each stage.

Search Strategy:

Medline (via OVID)

Terms	**Results**
exp Sinusitis/ or (sinusitis or rhinosinusitis or rhino-sinusitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	22,177
exp dilatation, pathologic/ or (dilat* or balloon* or catheter*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	411,168
sinuplast*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	61
(Sinusitis terms AND dilatation terms) OR sinuplasty	405
exp models, economic/ or cost.mp. or costs.mp. or economic*.mp. or cost-analysis.mp. or exp economics/ or insurance.mp. or exp insurance/ or reimburs*.mp. or claim.mp. or claims.mp. or charge*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	987,449
Sinusitis dilation terms AND economic terms	**20**
Limits: English, 2010 to present	**13**

Embase (via OVID)

Terms	**Results**
exp sinusitis OR exp rhinosinusitis	37453

exp balloon catheter/ or exp ballooon dilatation/ or (dilat* or balloon* or catheter*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	600785
sinuplast*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	117
(Sinusitis terms AND dilatation terms) OR sinuplasty	823
(model or models or modeling or modelling or cost or costs or cost-analysis or economic* or insurance* or reimburs* or claim or claims or charge*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4549647
Sinusitis dilation terms AND economic terms; Limits: English, 2010 to present	**89**

Medline (via Pubmed)

Terms	**Results**
Search (((((("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*))) AND (("Sinusitis"[Mesh] OR sinusitis OR rhino-sinusitis OR rhinosinusitis)))) OR sinuplast*)) AND (models, economic [mh] OR "costs and cost analysis" [mh] OR economics [mh] OR insurance [mh] OR model or models or modeling or modelling or cost or costs or cost-analysis or economic* or insurance* or reimburs* or claim or claims or charge*) Sort by: PublicationDate Filters: Publication date from 2010/01/01 to 2016/12/31; English	**22**

NHS EED (via CRD website): Total references: **10**

Search results:

Total number of references downloaded: 134

Rejected references (exclusion criteria) and duplicates removed: 96

Clinical Studies, Case Reports: 17

NHS EED Articles: 6

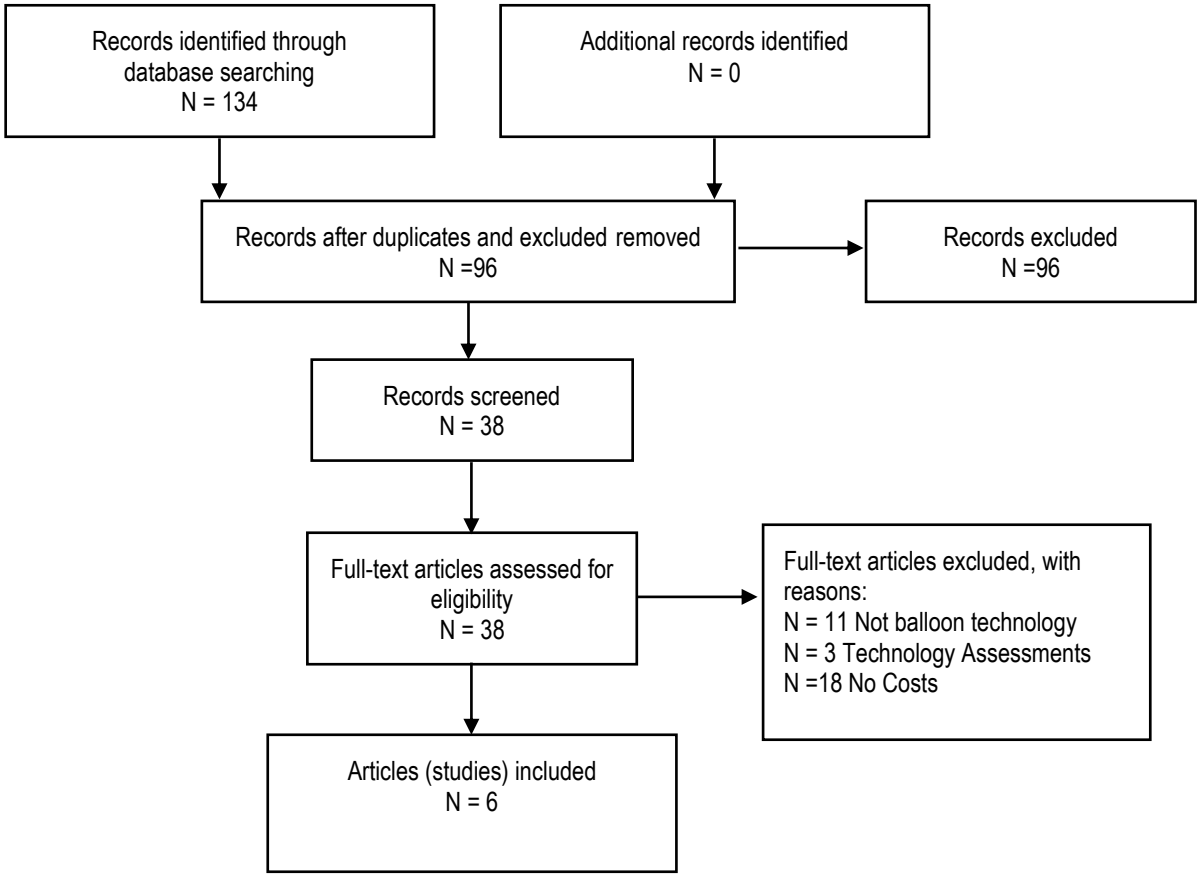
Review Articles: 12

Technology Assessment articles: 3

Total number of references for review: 38

The process flow for the study search and selection for published studies is presented below.

Studies selection flow



Thirty eight titles identified through the literature search were reviewed and articles were selected for further consideration based on the criteria listed in C1-8. No other articles were identified that were in the scope of the search timeframe and included in the analysis.

After full text review against the selection criteria noted in Table C1-8., a total of 32 of the 38 articles were excluded from the analysis. Of the 32, 11 articles did not utilize balloon sinus dilation technologies (e.g. Foley catheter, steroid-eluting stents).Three were Technology Assessments that did not contain any full economic evaluation studies for the XprESS System or any comparator balloon technology. And, the other eighteen studies suggested that the costs of balloon sinus dilation procedures may compare favourably, however no actual costs were reported in these studies.

A total of six articles were selected as meeting the inclusion criteria by reporting cost and or economic data for balloon sinus dilation (BCD) and FESS.

The studies included two budget impact analysis (Holy et al., 2013, Sorgeloose et al., 2012), two systematic reviews (McElroy et al., 2011, Smith et al.,2014) and two cross-sectional analysis based on ambulatory surgery claims database (Ference et al., 2014, Ference et al., 2015).

In regards to the two studies involving the ambulatory surgery claims database, the studies were conducted in the USA in 2011 which was the first year that standalone BCD codes were reported. Since the codes were new and the studies were based on claims data, these studies are likely to have limitations that should be taken into consideration both from a coding perspective and interpretation of outcomes. As outcomes of these queries are always dependent on proper coding at time of data entry there is a greater risk of errors when the codes were new. Similarly as surgeons gain experience they become more adept with the technique therefore outcomes for a newly introduced device are likely to improve over time.

The selected studies is presented below, which provides a summary list of all evaluations that reported costs.

The search did not yield any relevant high-quality economic evaluation/cost effectiveness evidence for the XprESS Multi-Sinus Dilation System or comparison with the comparator for the treatment of chronic rhinosinusitis identified in the literature.

Copies of the selected publications listed are provided in Attachment 4 of this submission.

8.2 Description of identified studies

Summary list of all evaluations involving costs

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs *(intervention and comparator)*	*Patient outcomes*	*Results*
Study 1 (2013) ***Budget impact analysis of balloon dilation and functional endoscopic surgery-a US payer perspective (ISPOR 18th Annual International Meeting New Orleans, LA United States. Conference)*** ***(Holy et al.)***	USA	Budget impact analysis Total member population (different for each US payer). Percentage of patients undergoing FESS that may switch to BCD. Of those switching to BCD, the percentage of patients undergoing BCD in the office.	Patients with chronic rhinosinusitis	In lieu of costs, all payments were derived from US claims databases including medical costs associated with CRS after failure of medical management. Payments include: surgical cost, post-operative care, rates of adverse events (AEs), recurrence of CRS, and revision surgery. All payment costs are specific to surgical type and rates of utilization are based on published evidence.	Example of model inputs for a payer covering a 10,000,000 member population. By adjusting the procedure mix and site of care, the overall cost of treatment for this particular patient population would be reduced by $3.8M (equivalent to 2.8% of total spending) in the 2-year time frame following a surgical intervention.	A Monte-Carlo analysis to account for uncertainty in assumptions. A budget impact analysis of BCD demonstrated that, for well selected patients, shifting the site of care from the operating room (OR) to the office, along with the less-invasive BCD technology vs. FESS, showed trends of lower cost over a 2-year horizon. Confirmed trend of lower cost for surgical case mix with increased ratio of BCD vs. FESS.

Study 2 (2012) ***Budget impact analysis of balloon sinuplasty versus classic functional endoscopic sinus surgery. Using a budget impact model to identify country specific market access strategy (ISPOR 15th Annual European Congress Berlin Germany).*** ***(Sorgeloose et al.)***	Germany	Budget impact model was designed to compare different cost scenarios for several years from the Germany government perspective with different caseload mix of FESS and BCD. Total cost of care for the surgical population was determined based on various scenarios: Timeline could be modified to include 1, 2 or 5 years; Different surgical intervention could be selected; Care setting and the impact of shifting site of care could be analyzed by changing the assumptions for inpatient/outpatient, in hospital/in office.	Patients with chronic rhinosinusitis	Model inputs included both unit costs and frequency of: All drugs and treatments related to medical management; Surgical procedure costs for FESS or BCD; Serious adverse events as a function of the surgical procedure; Rate of disease recurrence and revisions, based on surgical procedure. Publicly available costs (DRG) were obtained from German government websites.	Using Germany as a case example, the total population electing surgery was estimated at 81, 426 patients. Based on the 3 scenarios, the surgery accounted for more than 50% of total cost and was the main cost driver, followed by post-procedure treatments. Increased surgery rates by patients currently selecting medical management could increase total cost for all scenarios to close to € 1BN, with FESS showing trends of being the most expensive option in all cases.	Input variables with greatest uncertainty (i.e., percent patients electing surgery, rates of adverse events and revision rates) were identified and Monte-Carlo simulations were ran to determine total cost based on triangular distribution of those parameters. BCD was assumed to be performed in an outpatient setting and was shown to be favorable vs. FESS. Noted that if BCD could be done in the office setting under local, the potential cost-savings may be considerable.

Study 3 (2011) ***A systematic review of chronic rhinosinusitis in asia-pacfic and the role of balloon sinuplasty (ISPOR 14th Annual European Congress Madrid Spain)*** ***(McElroy et al.)***	Asia-Pacific region (Australia, China, India, Japan and Korea)	Three systematic reviews of the literature (epidemiological, clinical and economic) were undertaken to identify: 1. prevalence of CRS in the region, 2. clinical evidence for BCD, and 3. economic evidence for CRS. Purpose was to obtain information to inform a budget impact model for BCD in these countries. The search was performed from October 2010 through to February 2011.	Patients with chronic rhinosinusitis	Economic Studies: Ten economic studies confirmed high economic burden of CRS. One economic study on BCD was identified. (Friedman et al.2008) USA payer perspective, demonstrated a lower cost of BCD compared to FESS, predominantly due to the lower cost of revision surgery, associated shorter surgical time and higher rates of local anaesthesia use. Average cost of surgery per procedure was based on hospital charges (primary or revision): BCD= US $12,566 and FESS = US $14,471; p=0.013. Friedman M et al. Am J Rhinol. 2008; 22(2):204-9.	Epidemiological Studies: Estimate of prevalence of CRS in the Asia-Pacific Region: Australia 9-9.2% China-5-15% India-7.1%,.09% polyps Japan-.05%, 3-4% children Korea-1-7.1% Clinical Studies: BCD was reported to be favourable in terms of safety and efficacy with high ostia patency, shorter recovery time, improved symptoms and patient satisfaction.	Traditional literature searches provide limited information on the prevalence of CRS in Asia-Pacific. BCD appears to have value both clinically and economically. However, further research required to accurately quantify the economic benefits.

Study 4 (2015) ***Operative utilization of balloon versus traditional endoscopic sinus surgery.*** ***(Ference et al.)***	USA	Cross-sectional analysis based on State Ambulatory Surgery Claims Database 2011 in 4 states (CA, FL, MD, and NY). Cases were identified by CPT codes as BCD or FESS. 2011 was the first year for the standalone BCD codes. Patient demographics, surgical center and surgeon volume, mean charge, and operating room (OR) time were compared. No specific balloon device was mentioned.	Adult patients with chronic rhinosinusitis, patients >18 years	Costs were calculated on total hospital facility charges excluding physician fees, including surgeon and anesthesiologist. The number of sinuses procedures per case was calculated as the count of the sinuses operated upon (range 1-4). The database did not distinguish between unilateral or bilateral. FESS vs BCD used for at least one sinus/ combined surgery with or without FESS. Only the dataset for NY contained OR time.	BCD was used in 8.0% of the cases in 2011. 4.6% maxillary, 5.6% sphenoid, and 13.9% frontal BCD during maxillary sinus-only surgery resulted in a 37.3% increase in total charge (P<.001), and no significant difference in OR time compared to FESS. BCD during mini-ESS and pan-ESS resulted in 31.4% and 18.5% increase, respectively, in total charge (P<.001, P<.001), and 14.7% decrease in OR time for mini-ESS OR time, no statistically significant difference in pan-ESS OR time.	BCD in the OR were on average more expensive compared to FESS with minimal decrease in operating room time. OR Mean Times(min.): BCD/ Combined vs. FESS Maxillary 75 76 Mini-FESS 82 90 Pan-FESS 117 111 All FESS 93.5 92 Possible limitations of this study include: indication/severely, whether surgery was primary or revision, inability to distinguish unilateral from bilateral when comparing each side. Data do not capture in-office BCD under local which may prove to be cost-effective and time-efficient Further studies are necessary to compare the costs of in-office BCD to resource utilization of surgical management in the OR.

Study 5 (2014) ***Current utilization of balloon dilation versus endoscopic techniques in pediatric sinus surgery.*** ***(Ference et al.)***	USA	Cross-sectional analysis based on State Ambulatory Surgery Claims Database 2011 in 4 states (CA, FL, MD, and NY), cases were identified by CPT codes as BCD or FESS. 2011 was the first year for the standalone BCD codes. Patient demographics, surgical center and surgeon volume, mean charge, and operating room (OR) time were compared. No specific balloon device was mentioned.	Pediatric patients with chronic rhinosinusitis, patients < than 18 years	Costs were calculated on total hospital facility charges excluding physician fees: surgeon and anesthesiologist. The number of sinuses procedures per case was calculated as the count of the sinuses operated upon (range 1-4). The database did not distinguish between unilateral or bilateral. FESS vs BCD used for at least one sinus/ combined surgery with or without FESS Hybrid. Only the dataset for NY contained OR time. Pediatric patients undergoing concurrent adenoidectomy had greater odds of having BCD.	BCD was used in 11.9% of pediatric sinus surgery in 2011, 10.6% maxillary, 8.4% sphenoid, 11.8% frontal Median charges for maxillary antrostomy alone by BCD (P = .042) or with adenoidectomy (P \ .001) were $2100 and $4200 greater than FESS. However, OR time was similar (P = .81) between patients undergoing maxillary antrostomy, regardless of whether BCD was used, but was longer (P\.001) in those undergoing maxillary antrostomy and adenoidectomy when BCD was utilized. BCD, 47.2% included concomitant adenoidectomy.	BCD had higher average charges with no decrease in OR time vs. FESS. OR Mean Times(min.): BCD/ Combined vs. FESS Maxillary 78 80 Maxillary/adenoidectomy 80 42 *The OR time for maxillary FESS/ adenoidectomy is less which may represent possible miscoding.(antral lavage vs. maxillary antrostomy) Possible limitations include: indication/severely, whether surgery was primary or revision, inability to distinguish unilateral from bilateral when comparing each side. Future research is necessary to evaluate BCD improved outcomes and eventually decreased OR time for pediatric patient.

Study 6 (2014) ***Cost of adult chronic rhinosinusitis: A systematic review.*** ***(Smith et al.)***	USA	Systematic Review Included articles were categorized into seven domains: 1) overall healthcare cost (direct and indirect), 2) resource utilization, 3) medical management strategies, 4) overall procedure cost of endoscopic sinus surgery (FESS), 5) intraoperative technologies, 6) ESS litigation, and 7) CRS diagnostics.	Adult Patients with chronic rhinosinusitis	Reported a monetary cost associated with a defined intervention used to manage adult CRS. To maintain a common currency for comparison, all costs were converted to 2014 (USD) using an inflation calculator in September 2014. It is key to define the overall procedural cost of FESS to guide economic evaluations. The cost of FESS varies significantly depending on the country, The cost of FESS in the US, based on average hospital charges ($8,000 per case) is more than double the Canadian costs ($3,500 per case) and nearly 5 to 8 times the cost in other countries. This variance is possibly due to different types of third-party payers in the US vs. a universal payer	Four studies evaluating the cost of balloon dilation during the management of CRS were identified under intraoperative technologies. Overall, there was substantial heterogeneity between studies, and most reported hospital charges rather than true costs, which makes it very challenging to provide any meaningful conclusions. It is important for physicians to critically evaluate the increase in effectiveness in context with the additional cost to the healthcare system. More high-quality studies evaluating the cost impact of new technologies on the payers of healthcare are needed.	Future research on balloon dilation technology should provide micro-costing outcomes per case to accurately evaluate the added technology cost in context of the effectiveness outcomes. Future studies should focus on reporting true payment costs based on a well-defined cost perspective rather than reporting management charges.

8.2.1 Provide a complete quality assessment for each health economic study identified.

Quality assessment of health economic studies

1.-Study name: Budget impact analysis of balloon dilation and functional endoscopic surgery-a US payer perspective (ISPOR 18th Annual International Meeting New Orleans, LA United States. Conference). *(Holy et al.)*		
Study design	Budget impact analysis(BIM), sponsored by Acclarent	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	yes	Budget impact analysis performed on impact (BCD compared to FESS) for the entire surgical cohort with the German market. However, the BIM is locally adaptable and therefore includes input variables specific for each market
2. Was the economic importance of the research question stated?	yes	The study aimed to analyse and demonstrate the economic beneficial impact of an innovation for payers (governments, private payers) and Health Technology Assessments (HTAs).
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	Validity and value of budget impact analysis stated
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	BCD was compared to FESS
5. Were the alternatives being compared clearly described?	yes	Technology demonstration outlined in figure 1 & 2
6. Was the form of economic evaluation stated?	yes	Conducted Budget Impact Analysis. Calculated total cost of care to a specific payors over several year
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	The aim was to consider the budget impact from a payer perspective, thus this type of analysis was appropriate.
8. Was/were the source(s) of effectiveness estimates used stated?	yes	Data regarding clinical outcomes were sourced from small RCTs or single-arm prospective cohorts
9. Were details of the design and results of the effectiveness study given (if based on a single	yes	

study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	no	No large randomized controlled trials (RCT) exist comparing FESS to BCD. All Data regarding clinical outcomes are based on small RCTs or single-arm prospective cohorts
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	yes	Inputs included frequency and unit costs of preoperative work-ups (such as office visits and diagnostic procedures), index in- or out-patient surgery, frequency and unit cost of treatment for post-operative complications, post-operative procedures and relapse/reoperation rates. However, there is no mention of the cost of the device vs. FESS
13. Were the details of the subjects from whom valuations were obtained given?	not clear	This was not reported in the manuscript
14. Were productivity changes (if included) reported separately?	not clear	This was not reported in the manuscript
15. Was the relevance of productivity changes to the study question discussed?	yes	
16. Were quantities of resources reported separately from their unit cost?	not clear	
17. Were the methods for the estimation of quantities and unit costs described?	no	
18. Were currency and price data recorded?	yes	
19. Were details of price adjustments for inflation or currency conversion given?	no	Not applicable
20. Were details of any model used given?	yes	A Monte-Carlo analysis to account for uncertainty in assumptions confirmed trends of cost favorability for surgical case mix with increased ratio of BCD vs. FESS
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	Using the ISPOR best practices
22. Was the time horizon of cost	yes	

and benefits stated?		
23. Was the discount rate stated?	no	
24. Was the choice of rate justified?	no	
25. Was an explanation given if cost or benefits were not discounted?	no	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	not clear	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	no	
31. Was an incremental analysis reported?	no	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	yes	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
2.-Study name: *Budget impact analysis of balloon sinuplasty versus classic functional endoscopic sinus surgery. Using a budget impact model to identify country specific market access strategy (ISPOR 15th Annual European Congress Berlin Germany). (Sorgeloose et al.)*		
Study design	Budget impact analysis(BIM)), sponsored by Acclarent	
Study question	**Response (yes/no/not**	**Comments**

	clear/N/A)	
1. Was the research question stated?	yes	Budget impact analysis performed on impact(BCD compared to FESS) for the entire surgical cohort with US payors
2. Was the economic importance of the research question stated?	yes	Cost and efficacy gains to patients, providers and payors
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	Validity and value of budget impact analysis stated
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	Reference stated on safety and efficacy of BCD
5. Were the alternatives being compared clearly described?	yes	Technology demonstration outlined in figure 1 & 2. The parameters tab allowing users to select a market– all prevalence and incidence fields are then filled in based on assumptions captured within the model.
6. Was the form of economic evaluation stated?	yes	Cost of treatment analysis for CRS patients undergoing either FESS or BCD. Calculated total cost of care to a specific payors over 2 –years
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	Form of analysis was aligned with the study aim
8. Was/were the source(s) of effectiveness estimates used stated?	yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	no	Limitations of this model include the lack of randomized head to head studies comparing the BSP and traditional FESS surgical approaches. It therefore cannot be ruled out that the differences in outcomes/costs between the surgical techniques resulted from different baseline characteristics of the populations under study, and not the surgical approach used.
11. Were the primary outcome measure(s) for the economic	yes	

evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?	yes	Input variables with greatest uncertainty (i.e., percent patients electing surgery, rates of adverse events and revision rates) were identified and Monte-Carlo simulations were ran to determine total cost based on triangular distribution of those parameters. However, there is no mention of the cost of the device vs. FESS
13. Were the details of the subjects from whom valuations were obtained given?	not clear	
14. Were productivity changes (if included) reported separately?	not clear	
15. Was the relevance of productivity changes to the study question discussed?	yes	
16. Were quantities of resources reported separately from their unit cost?	not clear	
17. Were the methods for the estimation of quantities and unit costs described?	yes	Unit costs and frequency were tailored to each local market represented within the model, so that the final output of the model would be market-specific.
18. Were currency and price data recorded?	yes	Publicly available costs (DRG) were obtained from respective government / payer websites. Unit costs and frequency were tailored to each local market represented within the model, so that the final output of the model would be market-specific.
19. Were details of price adjustments for inflation or currency conversion given?	no	
20. Were details of any model used given?	yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	Using the ISPOR best practices
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	yes	
24. Was the choice of rate justified?	yes	

25. Was an explanation given if cost or benefits were not discounted?	yes	No discounting was assumed in the model as the timeframe for the analysis was short (≤5 years.)
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	not clear	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	no	
31. Was an incremental analysis reported?	no	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	yes	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
3-Study name: *A systematic review of chronic rhinosinusitis in asia-pacfic and the role of balloon sinuplasty (ISPOR 14th Annual European Congress Madrid Spain). (McElroy et al.)*		
Study design	Systematic review, sponsored by Acclarent	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research	yes	

question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	no	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	no	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	no	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	no	
12. Were the methods used to value health states and other benefits stated?	no	
13. Were the details of the subjects from whom valuations were obtained given?	no	
14. Were productivity changes (if included) reported separately?	no	
15. Was the relevance of productivity changes to the study question discussed?	no	
16. Were quantities of resources reported separately from their unit cost?	no	
17. Were the methods for the estimation of quantities and unit costs described?	no	

18. Were currency and price data recorded?	no	
19. Were details of price adjustments for inflation or currency conversion given?	no	
20. Were details of any model used given?	no	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	no	
22. Was the time horizon of cost and benefits stated?	no	
23. Was the discount rate stated?	no	
24. Was the choice of rate justified?	no	
25. Was an explanation given if cost or benefits were not discounted?	no	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	no	
27. Was the approach to sensitivity analysis described?	no	
28. Was the choice of variables for sensitivity analysis justified?	no	
29. Were the ranges over which the parameters were varied stated?	no	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	no	
31. Was an incremental analysis reported?	no	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	no	
33. Was the answer to the study question given?	no	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	Traditional literature searches provide limited information on the prevalence of CRS in Asia-Pacific. BSP appears to have value both

		clinically and economically. Additional research will further quantify this.
36. Were generalisability issues addressed?	yes	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

4.-Study name: *Operative utilization of balloon versus traditional endoscopic sinus surgery. (Ference et al.)*

Study design	Cross-sectional analysis	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	

12. Were the methods used to value health states and other benefits stated?	yes	State Ambulatory Surgery Claims Databases.
13. Were the details of the subjects from whom valuations were obtained given?	no	
14. Were productivity changes (if included) reported separately?	no	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	no	
17. Were the methods for the estimation of quantities and unit costs described?	no	
18. Were currency and price data recorded?	yes	Hospital charges/ amount in USD
19. Were details of price adjustments for inflation or currency conversion given?	no	
20. Were details of any model used given?	yes	Kolmogorov-Smirnov test statistic, Poisson regression analysis Generalized Linear Mode
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	no	
24. Was the choice of rate justified?	no	
25. Was an explanation given if cost or benefits were not discounted?	no	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	yes	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were	no	

appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?	no	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
5.-Study name: *Current utilization of balloon dilation versus endoscopic techniques in pediatric sinus surgery. (Ference et al.)*		
Study design	Cross-sectional analysis	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	yes	

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	yes	State Ambulatory Surgery Claims Databases.
13. Were the details of the subjects from whom valuations were obtained given?	no	
14. Were productivity changes (if included) reported separately?	no	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	no	
17. Were the methods for the estimation of quantities and unit costs described?	no	
18. Were currency and price data recorded?	yes	Hospital charges/ amount in USD
19. Were details of price adjustments for inflation or currency conversion given?	no	
20. Were details of any model used given?	yes	Kolmogorov-Smirnov test statistic, Poisson regression analysis Generalized Linear Mode
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	no	
24. Was the choice of rate justified?	no	
25. Was an explanation given if cost or benefits were not discounted?	no	

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	yes	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	no	
31. Was an incremental analysis reported?	no	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

6.-Study name: *Cost of adult chronic rhinosinusitis: A systematic review. (Smith et al.)*

Study design	Systematic review	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions	yes	

compared?		
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	yes	
13. Were the details of the subjects from whom valuations were obtained given?	no	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	yes	
17. Were the methods for the estimation of quantities and unit costs described?	yes	
18. Were currency and price data recorded?	yes	
19. Were details of price adjustments for inflation or currency conversion given?	yes	
20. Were details of any model used given?	no	

21. Was there a justification for the choice of model used and the key parameters on which it was based?	NA	
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	yes	
24. Was the choice of rate justified?	yes	
25. Was an explanation given if cost or benefits were not discounted?	yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	NA	
27. Was the approach to sensitivity analysis described?	NA	
28. Was the choice of variables for sensitivity analysis justified?	NA	
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	no	
31. Was an incremental analysis reported?	no	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	NA	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

This cost consequence analysis (CCA) aims to estimate the cumulative difference in costs and consequence per patient undergoing surgery for CRS, comparing surgery with standalone XprESS BCD (hereby referred to as XprESS) to surgery with FESS or standalone Acclarent BCD for (herby referred to as Acclarent) in average risk patients attending for CRS surgery in England.

This de novo economic analysis was conducted to support a submission to the National Institute of Health and Clinical Excellence (NICE) Medical Technology Evaluation Programme (MTEP) process as no other economic evaluations were identified comparing XprESS to FESS or Acclarent from an NHS England perspective. As such, all cost and outcomes are considered from a NHS England perspective.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

The base-case analysis considers an average risk patient attending for CRS surgery, where multiple sinuses are treated in one NHS episode of care. The HES databases for NHS England reports that a surgical interventions for CRS may include up to 7 procedures, with an on average episode of care comprising of 2.75 procedures (HSCIC). The base-case scenario will therefore consider a surgery involving multiple procedures (treating both sides) in one episode of care.

Sub-groups are not be explicitly analysed in the model as the clinical and economic benefits of XprESS relative to both comparators are relevant for all subgroups. There may be differences in procedure times and length of stay across subgroups, but the relative difference between XprESS and its comparators is expected to be constant. The findings of this analysis are therefore assumed to be relevant to all sub-groups where XprESS has an indication, including:

- Patients with uncomplicated chronic rhinosinusitis (or uncomplicated recurrent acute rhinosinusitis)
- Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis), with orbital or intracranial involvement
- Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) with and without nasal polyps
- Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) affecting the anterior ethmoid sinus in addition to maxillary, frontal or sphenoid sinus disease
- Patients with anatomic variants such as septal deviations and accessory ostia
- Children and young people under 18 years of age the outcomes are not expected to vary by subgroups.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

FESS is considered the standard surgical option for CRS surgery, as this accounts for the majority of surgeries in England. More recently BCDs entered this market as an alternative treatment option. The clinical practice and pathway of care is similar to that of FESS in that the CRS patient who has failed maximum medical management would be referred to the specialist community/ENT Consultant surgeon to perform the procedure on the appropriate sinus (es).

The therapeutic intent of both FESS and balloon dilation is to improve patient quality of life through relief of persistent symptoms by enlarging the natural drainage pathways (ostia) of the affected sinuses to restore mucus flow and ventilation.

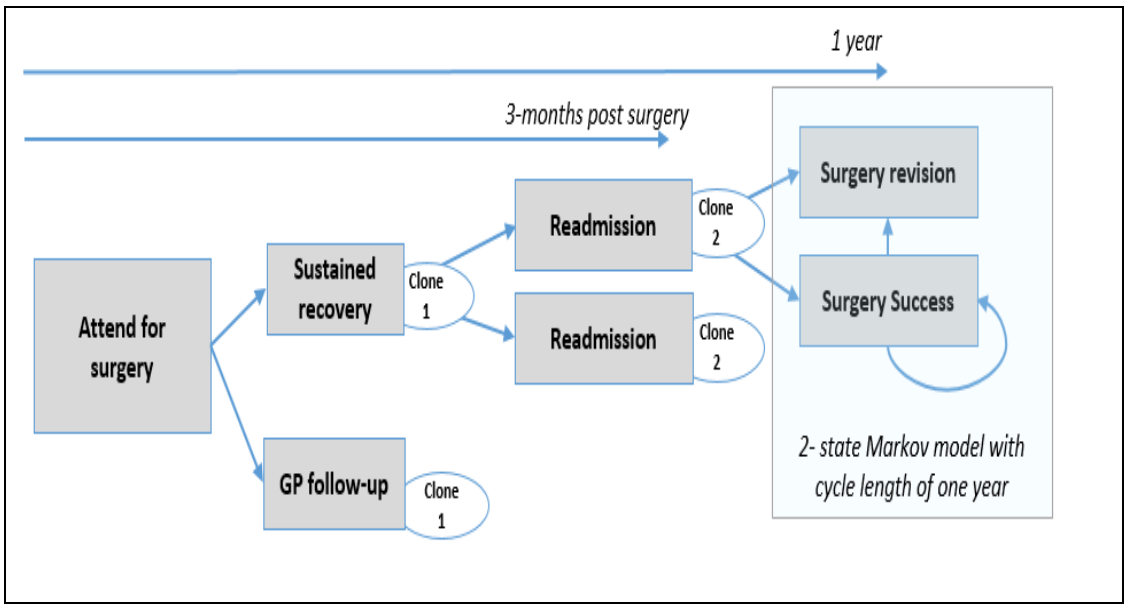
A full description of FESS, BCDs, the Acclarent and XprESS are detailed in section 1.3 of the technical document in Attachment 1 of this submission.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

The model structure is based on a published budgeted Impact model structure comparing BCDs with FESS (Holy et al., 2013) and comprises of a decision tree followed by a two state Markov model. The decision tree captures costs and outcome in the first year and the Markov structure captures costs and outcomes between years 2 and 5, applying a one year cycle length. The model structure is illustrated below.

Model Structure



9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The model structure was designed to capture costs and outcomes in a UK real world setting. Thus the model structure was based on outcomes reported in follow up of UK patients that had CRS surgery that had an impact of healthcare resource utilisation.

The 2003 audit of CRS patients in England found that only 43.4% of sinus-only patients reported their symptoms as much better at 12-months, while 31.9% felt their symptoms to be the same or worse than before surgery. As a result 4.7% had revision surgery and a further 5.6% were on waiting lists at 12 months. (Brown et al., 2003). This audit also reported that 42% of patients required GP follow up and 4.1% required hospital readmission within 90 days of CRS surgery with FESS.

As such, the model structure was designed to capture the following differences in costs:

- Hospital resources to conduct the procedure and manage recovery up until discharge, including equipment costs

- NHS resources to manage further treatment in the three months post-discharge, including prescription pain medication, GP visits and hospital readmissions
- NHS resources to manage repeat CRS episodes and surgery revisions

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

A cohort of patients progress through the model as follows:

- Patients enter the model having a CRS surgery for one of the indications specified for XprESS above. Costs in the initial health state are considered up to the point of discharge. This is expected to capture all differences related to the procedure cost
- Within the first three months post-discharge patients could have a sustained recovery or require one of more GP visits. This is aligned with the findings of the UK audit (Brown et al. 2003)
- Within the first 3 months patients are also at risk of readmission. This risk is assumed to be independent of if they require a GP visit. This is because there was no data on the relationship between the proportion of patients accessing GP services and readmitted to hospital.
- Beyond 3 months patients may transition to one of two mutually exclusive Markov health states, where they have a surgery revision or sustain recovery. Surgery revision is an absorbent health states as it is assumed that patients can only have one revision surgery. This is because the number of patients expected to have more than one revision surgery in this time horizon is expected to be low
- Irrespective of if patients have a revision surgery, all patients continue to be at risk of CRS episodes, albeit at a much lower rate than before surgery. This is aligned with the findings of the UK audit
- Mortality is not considered in the model as the model time horizon is a maximum of 5 years and CRS-related mortality is very rare and not expected to differ by intervention.

9.1.7 Define what the model's health states are intended to capture.

- **Surgical procedure:** Cost of time in theatre, equipment cost and recovery costs up to the point of discharge
- **GP Follow up:** Includes the cost of GP visits within 90 days of discharge plus the cost of pain medication at discharge
- **Sustained recovery:** Includes the cost of main medication at discharge
- **Readmission:** Includes the cost of readmission within 90 days of discharge
- **Surgery Success:** Includes on-going cost of GP visits for CRS events post-surgery
- **Surgery Revision:** Includes a one-off cost at transition for a revision surgery, plus on-going cost of GP visits for CRS events post-surgery

A full description of the approach to calculating the transition probabilities and costs for each health state is detailed below.

Surgical Procedure cost

Two approaches are applied to calculate the cost of a surgical procedure, excluding equipment. The base-case approach assumes all procedures are conducted in theatre under general anaesthesia, while the alternative option considers the impact if a proportion of surgeries are conducted under local anaesthesia in the ambulatory setting.

The cost of a general surgical procedure was calculated as the surgical time multiplied by the unit cost of theatre and staff time, plus the theatre consumable used during the procedure and the time spend in hospital post-surgery.

In the second approach, the cost of a surgery conducted under local was estimated by applying a ratio of the cost of day case hernia surgical procedures conducted under general and local anaesthesia respectively(Zilvetti et al., 2009) and assuming there would be a similar proportional reduction in costs between CRS surgical procedures conducted under general switched to local. The cost of surgery was calculated as the weighted average, applying the proportion of surgeries expected to be conducted under general and local anaesthesia with each technology. For BCD devices, it was assumed that 60% of surgeries would be moved to local if XprESS was recommended in the guidelines, obtained from conservative assumptions supplied by UK experts. This compares with 90% of BCD surgeries currently conducted under local in the USA. For FESS, it was assumed that only 2% would be done under local as is current practice reported in the 2003 audit. This is consistent with USA data which reports that less than 5% of FESS procedures are performed under local. The inputs and sources applied are described in **Appendix 1 of the technical document** in Attachment 1.

The equipment costs were calculated separately and assumed to be the same irrespective of the anaesthesia option. Unit costs and quantities for the consumables required with each intervention were sourced from Entellus market data. No capital costs for equipment were included as all other capital equipment used is expected to be standard surgical equipment applicable to all technologies and included in the unit cost of theatre time. The inputs and sources applied in the surgical health state in the base case are described in **Appendix 1 of the technical document** in Attachment1.

Under both approaches the difference in surgical time was expected to be the main driver of the difference in cost. The base-case estimates were supplied by UK experts based on conducting multiple bilateral procedures in an episode of care. A scenario analysis applied the results of an Italian RCT based on only frontal sinuses. These estimate were consistent with procedure times reported in the USA from CMS database which show that for all sinus the surgical time was considerably longer with FESS compared to

BCDs and is even longer when treating multiple sinuses. A more detailed description of the selection inputs is provided in **Appendix 2** and the CMS procedure time data is provided in **Appendix 3 of the technical document** in Attachment 1.

GP follow-up 3-months post-discharge

The TP for requiring GP follow-up with FESS was obtained from the UK audit and TPs for XprESS and Acclarent were derived by multiplying the relative risk (RR) of discharge with nasal bleed by the TP for FESS. The risk of nasal bleed was selected to derive the RR as this expected to be a good indicator of the risk of requiring healthcare resources in the short-term.

The unit cost of a GP follow up was calculated as the unit cost of a GP visit and a prescription cost, both sourced from the PSSRU 2015(Curtis, 2015) plus a the unit cost of a prescription for a steroid nasal spray (Fluticasone propionate), a course of macrolide (Azithromycin 500 mg once daily for 3 days) and a course of macrolide (Azithromycin 500 mg once daily for 3 days)(BNF, 2016, 2016). The cost of a GP visit was multiplied by the average rate of GPs within 3 months amongst those with 1 or more visit. This rate was also obtained from the UK audit (Brown et al., 2003).

The cost of pain medication post-discharge was calculated as the days on pain medication sourced from the REMODEL RCT (Chandra et al., 2016) multiplied by the cost of pain medication per day.

A more detailed description of the GP follow-up 3 months post-discharge inputs is provided in **Appendix 1 of the technical document in** Attachment 1.

Readmission

Similarly, the TP for readmission after FESS was also obtained from the 2003 audit (Brown et al., 2003) which reported 4.1% of sinus patients were readmitted within three months. The same approach to adjusting the TP for

FESS to calculate the TP with XprESS or Acclarent as described above for GP visits was applied, using the RR of nasal bleed.

A more detailed description of the readmission inputs is provided in **Appendix 1 of the technical document in** Attachment 1**.**

Revision and Surgical Success Health States

The TP for surgery revision after FESS was obtained from the UK audit which reported 4.1% had a revision surgery by 12 months and 15.5% had revision surgery by 5 years (Hopkins et al., 2009). The TPs for surgery revision with XprESS and Acclarent were calculated applying a RR of surgery revision with XprESS compared to FESS using the outcomes from the REMODEL (Chandra et al., 2016) RCT at one year. An alternative selection option allows the user to apply the % with revision at 12 month reported in the REMODEL study directly to derive the TPs and assume that this TP is constant over time.

The cost of the revision surgery was assumed to be the same as the initial surgical procedure cost.

Both long-term health states also included monthly costs of GP visits. The monthly rate of GP visits with FESS was obtained from the UK audit (Hopkins et al., 2006). The rate of GP visits with XprESS and Acclarent was calculated using the percentage difference in the reduction in CRS episodes events reported in the REMODEL RCT and applying this proportional difference to the rate of GP follow-ups with. All rates of GP visits beyond 3 months were assumed to be constant over time and the unit cost of a GP visit was assumed to be the same as in the first three months. A monthly rate was applied and multiplied by 9 for the period between 3 and 12 months in the first year and multiplied by 12 for all subsequent years.

A more detailed description of the revision and surgical success inputs is provided in in **Appendix 1 of the technical document** in Attachment 1.

9.1.8 Describe any key features of the cost model not previously reported.

Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	5 years	The model time horizon is 5 years but most of the differences in cost are expected to accumulate in year 1. This time horizon was selected as this captures the medium-term differences in cost and outcomes. Costs were not captured beyond 5 years as audit data of patients with CRS surgery was only available for 5 years and there was too much uncertainty regarding the outcomes beyond this point 5 years.	NA
Discount of 3.5% for costs	3.5%	All costs beyond one year are discounted at a rate of 3.5% in accordance with NICE guideline for economic evaluation. No outcomes beyond 1 year are reported.	NA
Perspective (NHS/PSS)	NHS	The model reports costs from an NHS England perspective. This is aligned with the scope of the analysis	NA
Cycle length	1 year		
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Specific searches were not carried out to source clinical inputs, instead all clinical inputs were selected by Entellus in consultation with internal and external clinical experts. The sources selected included a combination of real-world studies of post-surgical outcomes amongst English patients and randomised controlled trials (RCTs) identified in the systematic literature review (SLR) conducted alongside this analysis, described in Section A.

As patients in the UK typically access surgery later which is associated with worse outcomes(Hopkins et al., 2015, Benninger et al., 2015), the baseline risk of requiring healthcare utilisation or revision surgery is expected to be higher than outcomes reported in RCTs. As noted above, the 2003 audit of CRS patients in England found 4.7% had revision surgery and a further 5.6% were on waiting lists at 12 months. (Brown et al., 2003). This compares with 2.7% and 6.9% requiring revision surgery within 12 months of surgery with XprESS and FESS respectively, as reported in a large, recently conducted RCT (Chandra et al., 2016).

To account for this difference in real world outcomes, healthcare resource utilisation in the FESS arm were sourced from the UK audit and outcomes with XprESS and Acclarent arm were estimated by applying either a relative risk or proportion adjustment using clinical trial data. At the time of this audit, FESS was the only surgical treatment available in England and as outcomes with FESS are not expected to have changed, the results of the UK audit are assumed to be representative of outcomes with FESS in a real-world English setting. Most of the clinical inputs to determine relative differences in outcomes between XprESS and FESS were sourced from the REMODEL RCT (Chandra et al., 2016), selected as the was the largest and most robust RCT identified by the SLR accompanying this research.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Similarly, specific searches were not carried out to source the cost inputs. Instead these were sourced from NHS references costs widely used in economic evaluations or internal market data collected by Entellus. All costs were vetted with UK experts and where there was uncertainty around the most appropriate sources to apply the model was programmed to select between multiple options.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome

linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Yes. The difference in nasal bleed at discharge was used to estimate relative difference in GP visits and hospital readmission 90 days post hospital admission. The approach to applying a relative risk to estimate the transition probabilities for these health states for each technology is described in section **9.1.7 above.**

Similarly, the difference in the change in CRS episodes at 12 months was used to estimate the rate of GP visits beyond 3 months. The approach to calculating the rates for each technology is also described in section **9.1.7 above**.

Similarly, the difference in revision rates at 12 months and annual beyond 12 months was estimated applying a relative risk reported in an RCT. The approach to calculating the rates for each technology is also described in section **9.1.7 above.**

9.2.4. Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The cost of adverse events was captured through the risk of GP follow-up, readmission and revision. The approach to calculating these transition probabilities and the costs of these health states is detailed in section **9.1.7 above.**

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

This is a critical step and the names and professional titles of the clinical advisers:

- Mr Peter Andrews – Royal National Throat Nose and Ear Hospital

- Mr David Roberts – Guys and St Thomas's Hospital
- Ms Claire Hopkins – Guys and St Thomas's Hospital
- Mr Ben Hunter – St George's Hospital

Details of the approach for seeking clinical expert opinion include:

- The criteria for selecting the experts: *The key thought leaders in the field of Sinus Disorders in the UK.*
- The number of experts approached: *4*
- The number of experts who participated: *4*
- Declaration of potential conflict(s) of interest from each expert or medical specialty whose opinion was sought: *None.*
- The background information provided and its consistency with the totality of the evidence provided in the submission: *Based on their experience in the field and the evidence discussed with the experts was referenced third party information.*
- The method(s) used to collect and collate the opinions: *Face to face discussions.*
- The medium used to collect opinions: *direct interview*
- The questions asked: *questions related to their knowledge around the time that it takes to do ESS, what medications they use pre and post op, the need for early intervention, the need to better educate primary care, the ability to move to an ambulatory surgery in their facility, their desire to do the BCD under local*
- Whether iteration was used in the collation of opinions and if so, how it was used: *When asking the experts the questions their answers were similar in nature and we built in some variances to account for real world.*
- The uncertainly around these values should be addressed in the sensitivity analysis. *Was discussed.*

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission.

All inputs applied in each health state are detailed below, along with a description of the input and the source. All inputs were varied by 20% in the sensitivity analysis.

Default inputs for surgical health state, under general

Input	Value	Reference
Procedure Time XprESS: The time in surgery with XprESS, reported in minutes	30 mins*	**Expert Opinion:** Option input that defaults to an assumption provided by UK experts, as this is expected to reflect current practice in the UK.
Procedure Time FESS: The time in surgery with FESS, reported in minutes	90 mins*	**Expert Opinion:** As above
Procedure Time Acclarent: The time in surgery with Acclarent, reported in minutes	40 mins*	**Expert Opinion:** As above
Average length of stay XprESS: The time in surgery with Acclarent, reported in minutes	0.43 days*	**HES data (HSCIC):** Option input that defaults to applying the length of stay with a E148 frontal sinus procedure.
Average length of stay with FESS	0.97 days*	**HES data (HSCIC):** As above
Average length of stay with Acclarent	0.43 days*	**HES data (HSCIC):** As above
Unit cost theatre time per min	£20*	**NHS Institute for Innovation and Improvement(III, 2009):** Option input that defaults to the average hourly operating cost of £1200 per theatre reported by the Institute for Innovation and Improvement
Unit cost surgeon's time per min	£1.76	**PSSRU 2015(Curtis, 2015)**: Surgical time per minute excluding qualification costs
Unit cost nurses time per min	£1.46	**PSSRU 2015(Curtis, 2015):** cost per minute of patient contact time with Band 5 nurse, excluding qualification costs
Unit cost of drapes & gowns per surgery: Unit cost of drapes and gowns used during 1 surgical procedure	£80	**Estimate.** Estimate based on list prices reported by Medisave.co.uk; Assuming drapes and gowns @ £40 for 1 surgeon and 1 nurse
Unit cost of tray /camera per surgery	£35	**NHS Institute for Innovation and Improvement(III, 2009):** report estimated cost of surgical trays cost £35 per surgery
Unit cost of tray /camera per surgery	£400	**Deltex Medical(2006):** report estimated the average cost of an NHS surgical bed was £400
Avg. equip cost per XprESS procedure: The average cost of all	£975	**Entellus Market data**: Includes the cost of one XprESS Balloon; costs sourced from ENTELLUS internal market data

consumable equipment used in a XprESS surgical procedure		
Avg. equip cost per FESS procedure: The average cost of all consumable equipment used in a FESS surgical procedure	£300	**Entellus Market data:** Includes the cost of one FESS Micro-blade and one burr; costs sourced from ENTELLUS internal market data
Avg. equip cost per Acclarent procedure: The average cost of all consumable equipment used in an Acclarent surgical procedure	£1141	**Entellus Market data:** Includes the cost of one Acclarent Balloon, 1 guide catheter, 1 lavage device and 1 inflation device; costs sourced from ENTELLUS internal market data

Default inputs for surgical health states, with local

Inputs	Value	Reference
% under local XprESS Refers to the proportion of surgeries expected to conducted under local and is only applicable if the input "Consider local anaesthesia" is toggled to "include local"	60%	Expert opinion
% under local FESS As above, refers to the proportion of surgeries expected to conducted under local with FESS	0%	Expert opinion
% under local Acclarent As above, refers to the proportion of surgeries expected to conducted under local with FESS Acclarent	60%	Expert opinion
Cost ratio between local and general anaesthesia procedures. Assumption for the cost ratio between surgical procedures conducted under local compared to general anaesthesia	0.631	**Zilvetti et al. 2009**(Zilvetti et al., 2009) Calculated as the ratio between the costs of a day case hernia procedures conducted under local (£640) and general (£1015) anaesthesia respectively
Unit cost of procedure under general - XprESS	£984	**Model Calculation**. Calculated as the time in surgery under general multiplied by the unit cost of theatre time, a surgeon's time and a nurse's time plus the cost of drapes, gowns and trays plus the average days in hospital after surgery with XprESS multiplied by the unit cost of a hospital day
Unit cost of procedure under general - Fess	£2594.00	**Model Calculation.** As above, applying the time in surgery with FESS and the

		average time in hospital after surgery with FESS
Unit cost of procedure under general - Acclarent	£1404.33	**Model Calculation.** As above, applying the time in surgery with Acclarent and the average time in hospital after surgery with Acclarent

Default inputs for GP follow-up health state

Inputs	Value	Reference
RR nasal bleed. This input is used to adjust the proportion of patients requiring a GP visit or hospital admission with FESS to calculate these inputs for FESS	0.57	**REMODEL RCT(Chandra et al., 2016)**. Derived from the results of the REMODEL RCT by dividing the risk of nasal bleed with XprESS by the risk of nasal bleed with FESS
% needing GP visits within 90 days - XprESS	24%	**REMODEL RCT(Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Calculated as the probability of a GP visits 3 months post-surgery with FESS, adjusted using the RR nasal bleed input
% needing GP visits within 90 days - FESS	42%	**UK Audit (Brown et al., 2003).** The probability of requiring a GP visit was sourced from Brown et al. 2003, based on the findings of a UK audit of CRS surgeries, where all surgeries were assumed be completed with FESS
% needing GP visits within 90 days - Accelerant	24%	Assumed to be the same as XprESS
Rate of GP visits in first 3 months	1.861	**UK Audit (Brown et al., 2003)** Calculated based on the proportion reported to attend the GP,1 to 3 or more times within 3 months of CRS surgery
Unit cost of GP visit	£94.43	**PSSRU 2015, BNF, Expert opinion.** Calculated as the unit cost of a GP visit and a prescription cost, both sourced from the PSSRU 2015 (Curtis, 2015) plus a the unit cost of a prescription for a steroid nasal spray (Fluticasone propionate), a course of macrolide (Azithromycin 500 mg once daily for 3 days) and a course of macrolide (Azithromycin 500 mg once daily for 3 days). Prescription assumptions were supplied by UK experts and prescription costs were sourced from the British National Formulary (BNF), 2016 (BNF, 2016, 2016)
Days on pain medication - XprESS	1	REMODEL RCT **(Chandra et al., 2016)**
Days on pain medication - FESS	2.8	REMODEL RCT **(Chandra et al., 2016)**
Days on pain medication -	1	Assumption. Assumed to be the same as

Accelerant		XprESS
Unit cost of pain medication	£0.13	**BNF, Expert opinion.** Assumed to be treated with 400mg Ibuprofen three times a day, an assumption provided by UK experts. Unit costs were obtained from the BNF, 2016

Default inputs for readmission health state

Inputs	Value	Reference
% readmitted – XprESS: The probability of a readmission for a nasal procedure within 3 months of CRS surgery with XprESS	2.3%	**REMODEL RCT(Chandra et al., 2016) & UK Audit (Brown et al., 2003).** Calculated as the probability of a readmission post-surgery with FESS, adjusted using the RR of nasal bleed
Transition probability readmitted - FESS	4.1%	**UK Audit (Brown et al., 2003).** The probability of readmission within 3 month of surgery was sourced from Brown et al. 2003, based on the findings of a UK audit of CRS surgeries, where all surgeries were assumed be completed with FESS
Transition probability readmitted - Accelerant	2.3%	Assumed to be the same as XprESS
Unit Cost per readmission	£601	**NHS Reference cost 2011-12**.**(Gov.uk, 2011-12)** Reference costs CZ12V – Minor Nose Procedures, 19 years and over with CC, reference price for non-elective admission. This year was selected for estimating the costs as prior to 2012-13 references prices were calculated as an average across hospitals

Default inputs for revision and surgery success health state

Items	Value	Reference
Percentage difference in rate of CRS event. Percentage difference in the rate of CRS event post-surgery with XprESS compared FESS. This input is used to adjust the proportion of patients requiring a GP visit between beyond 3 months	-13.5%	**REMODEL RCT (Chandra et al., 2016)** Derived from the results of the REMODEL RCT as the difference between the changes in CRS events with XprESS compared to FESS, divided by the change in CRS events with FESS
Monthly rate of GP visits beyond 3 months with XprESS	0.10	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Calculated as the monthly rate of GP visit with FESS beyond 3 months, adjusted using the percentage difference in the rate of CRS events. This rate is assumed to be constant over time
Monthly rate of GP visits beyond 3 months - FESS	0.12	**UK Audit (Brown et al., 2003)** Calculated using the proportion reported to attend the

		GP one to three or more times beyond three months of CRS surgery in the2003 UK audit (Brown et al. 2003). Annual rates were converted to monthly rates. This rate is assumed to be constant over time
Monthly rate of GP visits beyond 3 months - Acclarent	0.10	**Assumption.** Assumed to be the same as XprESS
REMODEL % with revision at 12 months - XprESS	1.4%	**REMODEL RCT (Chandra et al., 2016)** Obtained from the REMODEL RCT using the percentage with revision at 12 months following surgery with XprESS. This annual probability was assumed to be constant over time
REMODEL % with revision at 12 months - FESS	1.2%	**REMODEL RCT (Chandra et al., 2016)** As above, using the same measure reported for FESS.
REMODEL % with revision at 12 months - Acclarent	1.4%	**Assumption.** Assume to be the same as with XprESS
Relative risk of revision	.875	**REMODEL RCT (Chandra et al., 2016)** Calculated as the risk of revision with XprESS divided by the risk of revision with FESS, where both inputs are sourced from the REMODEL RCT
% with revisions at 12 months - XprESS	3.6%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Calculated as the annual probability with FESS multiplied by the relative risk of revision with XprESS
% with revisions at 12 months - FESS	4.1%	**UK Audit (Brown et al., 2003)** The base-case defaults to estimating outcomes in a UK setting. This rate for FESS was obtained from 1 year follow up of the UK audit (Brown et al. 2003)
% with revisions at 12 months - Acclarent	3.6%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Assumed to be the same as XprESS
Annual risk of revisions > 12 months - XprESS	3.3%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)**Calculated as the annual probability with FESS multiplied by the relative risk of revision with XprESS
Annual risk of revisions > 12 months - FESS	3.8%	**UK Audit (Brown et al., 2003)** This rate for FESS was obtained from 5 year follow up of the UK audit (Brown et al. 2003). The proportion that had a revision by one year was subtracted by the proportion that had a revision by 5 years and divided by 4 to derive an annual probability beyond 1 year
Annual risk of revisions > 12 months - Acclarent	3.3%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Assumed to be the same as FESS

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The table below provides a matrix of all tariffs used for CRS surgeries funded by NHS England.

	CZ14Y 14/15	**CZ14Y 15/16**	**CZ14V 14/15**	**CZ14V 15/16**
Tariff	£1,491	£1,398	£1,491	£1,463
Type	Combined	Combined	Combined	Combined
Trim Point	>5 = £235	>5 = £218		>5 = £218
AVG MFF		18%		18%
AVG Reference Cost		£1,381	£1,340	£1,340

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

Coding recommendations

Depending on which sinus the procedure is performed on one of the following OPCS-4 codes is assigned:

- E13.8 Other specified other operations on maxillary antrum
- E14.8 Other specified operations on frontal sinus
- E15.8 Other specified operations on sphenoid sinus
- E17.8 Other specified operations on unspecified nasal sinus

The following three codes are assigned directly after one of the codes listed above:

- Y76.1 Functional endoscopic sinus surgery
- Y40.3 Balloon dilation of organ NOC
- Y53.4 Approach to organ under fluoroscopic control

In addition an ICD-10 code from category J32. - Chronic sinusitis is assigned

Obtained from: *Balloon catheter dilation of paranasal sinus ostia for chronic sinusitis NICE interventional procedure guidance* [IPG273] http://www.nice.org.uk/guidance/ipg273

Additional coding information and mix of procedures is detailed in Attachment 3 of this submission.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Specific searches were not carried out to source the cost inputs. Instead these were sourced from NHS references costs widely used in economic evaluations or internal market data collected by Entellus. All costs were vetted with UK experts and where there was uncertainty around the most appropriate sources to apply the model was programmed to select between multiple options.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

- The criteria for selecting the experts: *Thought leaders within the UK market who are well respected amongst their peers.*
- The number of experts approached: 8
- Number of experts who participated: 8

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- Declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought: *1 clinician provided support in training of other colleagues.*
- The background information provided and its consistency with the totality of the evidence provided in the submission: *All background information for building the model and interpretation the model was obtained from literature identified through the SLR or provided by clinical experts.*
- The method(s) used to collect and collate the opinions: *Questions asked directly to the experts who then suggested third party clinical references.*
- The medium used to collect opinions: *Direct interview.*
- The questions asked: *Since time of the procedures were such an important value in the model the questions focused around this area: What is the recognised time taken to complete endoscopic sinus surgery? What clinical data is there to support this information?*
- Whether iteration was used in the collation of opinions and if so, how it was used the uncertainty around these values should be addressed in the sensitivity analysis: *When asking the experts the questions, their answers were similar in nature and we built in some variances to account for real world.*
- The uncertainty around these values should be addressed in the sensitivity analysis: *yes.*

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

Unit costs and quantities for the consumables required with each intervention were sourced from Entellus market data. No capital costs for equipment were included as all other capital equipment used is expected to be standard surgical equipment applicable to all technologies and included in the unit cost of theatre time. All unit cost for consumables included in the model are detailed in 9.3.5 in the table titled "Default inputs for surgical health state, under general"

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The average selling price in the UK is being used for the XprESS System and for the FESS Micro-blade and 1 bur.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model.

Costs per treatment/patient associated with the technology in the cost model – Cost for XprESS

Items	Value	Source
Price of the technology per treatment/patient	£900	The only cost applied is for the consumable cost
Consumables (if applicable)	£900	Includes the cost of one XprESS Balloon; costs sourced from ENTELLUS internal market data of average selling price in the UK.
Maintenance cost	£0	Not applicable, all equipment is consumable
Training cost	£0	All training is provided free of charge by XprESS
Other costs	NA	
Total cost per treatment/patient	£900	The only cost applied is for consumable costs

Costs per treatment/patient associated with the comparator technology in the cost model – Costs for FESS

Items	Value	Source
Cost of the comparator per treatment/patient	£300	The only cost applied is for consumable costs
Consumables (if applicable)	£300	Includes the cost of 1 FESS Micro-blade and 1 bur; costs sourced from ENTELLUS internal market data of the average selling price of £150 each
Maintenance cost	£0	All equipment is consumable
Training cost	£0	No training required
Other costs	NA	
Total cost per treatment/patient	£300	The only cost applied is for consumable costs

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

The cost for each health state vary by comparator. The unit costs for each input applied in each health state are detailed in Section **9.2.6 above**.

List of health states and associated costs in the economic model

Health states	Items	Value	Reference
Health state 1	**Technology cost**	Detailed in Section **9.2.6 above**	Detailed in Section **9.2.6 above**
	Staff		
	Hospital costs		
	[Other items]		
	Total		
Health state 2			

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost

model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The cost for all adverse events is captured in each health state. The unit costs for the adverse events captured in each health state are detailed in Section **9.2.6 above**.

List of adverse events and summary of costs included in the cost model

The cost of adverse events was captured through the risk of GP follow-up, readmission and revision. The approach to calculating these transition probabilities and the costs of these health states is detailed in section **9.1.7 above.**

All inputs, values and sources used to calculate the costs of adverse events are detailed in the tables provided in section **9.2.6 above**.

Adverse events	Items	Value	Reference
Adverse event 1	**Technology**	Detailed in Section **9.2.6 above**	Detailed in Section **9.2.6 above**
	Staff		
	Hospital costs		
	[Other items]		
	Total		
Adverse event 2	**Technology**		
	Staff		
Adverse event [X]			

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Not applicable. All costs are detailed in section **9.2.6 above.**

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable. All costs are detailed in section **9.2.6 above**.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

Uncertainty around the time horizon of the model was considered by reporting results over a 1,2,3,4 and 5 year time horizon. No other sensitivity analysis was considered for the structural aspects of the model as there was not expected to be any uncertainty around the patient pathway.

Extensive sensitivity analysis was conducted around the model inputs. This included conducting a deterministic sensitivity analysis (DSA), reporting the results of multiple scenario analyses by applying alternative sets of assumptions, and conducting a breakeven analysis around the procedure time with XprESS and FESS.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How variables varied and what

were was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Yes, a DSA was undertaken. The DSA varied each model input was one at a time and re-calculated the net difference in cost per patient to evaluate the impact that varying each input had on the base-case result for each technology. All primary clinical inputs were included in the DSA. The upper and lower bounds were calculated by applying a 20% increase and decrease respectively.

9.4.3 Summarise the variables used in the sensitivity analysis.

Variables used in one-way scenario-based deterministic sensitivity analysis

Input	Base-case	Low value	High value
Discount Rate	0.035	0.028	0.042
Procedure Time XprESS	30 mins	24 mins	36 mins
Procedure Time FESS	90 mins	72 mins	108 mins
Procedure Time Acclarent	40 mins	32 mins	48 mins
Average length of stay XprESS	0.43 days	0.34 days	0.52 days
Average length of stay FESS	0.97 days	0.78 days	1.16 days
Average length of stay Acclarent	0.43 days	0.34 days	0.52 days
% under local XprESS	60%	48%	72%
% under local FESS	2%	2%	3%
% under local Acclarent	60%	48%	72%
Unit cost theatre time	£ 20.00	£ 16.00	£ 24.00
Unit cost surgeon's time	£ 1.77	£ 1.41	£ 2.12
Unit cost nurse's time	£ 1.47	£ 1.17	£ 1.76
Unit cost of drapes & gowns per surgery	£ 80.00	£ 64.00	£ 96.00
Unit cost of tray /camera per surgery	£ 35.00	£ 28.00	£ 42.00
Unit cost per hospital day	£ 400.00	£ 320.00	£ 480.00
Cost ratio between local and general anaesthesia procedures	£ 0.63	£ 0.50	£ 0.76
Unit cost of procedure under general - XprESS	£ 984.00	£ 787.20	£ 1,180.80
Unit cost of procedure under general - FESS	£ 2,594.00	£ 2,075.20	£ 3,112.80
Unit cost of procedure under general - Acclarent	£ 1,216.33	£ 973.07	£ 1,459.60
Unit cost of procedure under local - XprESS	£ 620.45	£ 496.36	£ 744.54
Unit cost of procedure under FESS	£ 1,635.63	£ 1,308.50	£ 1,962.75
Unit cost of procedure under Acclarent	£ 766.95	£ 613.56	£ 920.34

Avg. equip cost per XprESS procedure	£ 900.00	£ 720.00	£ 1,080.00
Avg. equip cost per FESS procedure	£ 300.00	£ 240.00	£ 360.00
Avg. equip cost per Acclarent procedure	£ 1,141.45	£ 913.16	£ 1,369.74
RR nasal bleed	0.57	0.46	0.69
% needing GP visits within 90 days - XprESS	24%	19%	29%
% needing GP visits within 90 days - FESS	42%	34%	51%
% needing GP visits within 90 days - Acclarent	24%	19%	29%
Rate of GP visits in first 3 months	1.86	1.49	2.23
Unit cost of GP visit	£ 94.43	£ 75.54	£ 113.32
Days on pain medication - XprESS	1.00	0.80	1.20
Days on pain medication - FESS	2.80	2.24	3.36
Days on pain medication - Acclarent	1.00	0.80	1.20
Unit cost of pain medication	£ 0.13	£ 0.11	£ 0.16
% readmitted - XprESS	2%	2%	3%
% readmitted - FESS	4%	3%	5%
% readmitted - Acclarent	2%	2%	3%
Unit Cost per readmission	£ 601.00	£ 480.80	£ 721.20
Percentage difference in rate of CRS event	-14%	-11%	-16%
Monthly rate of GP visits beyond 3 months - XprESS	10%	8%	12%
Monthly rate of GP visits beyond 3 months - FESS	12%	9%	14%
Monthly rate of GP visits beyond 3 months - Acclarent	10%	8%	12%
REMODEL % with revision at 12 months - XprESS	1.4%	1.1%	1.7%
REMODEL % with revision at 12 months - FESS	1.6%	1.3%	1.9%
REMODEL % with revision at 12 months - Acclarent	1.4%	1.1%	1.7%
Relative risk of revision	0.88	0.70	1.05
% with revisions at 12 months - XprESS	3.6%	2.9%	4.3%
% with revisions at 12 months - FESS	4.1%	3.3%	4.9%
% with revisions at 12 months - Acclarent	3.6%	2.9%	4.3%
Annual risk of revisions > 12 months - XprESS	2.5%	2.0%	3.0%
Annual risk of revisions > 12 months - FESS	2.9%	2.3%	3.4%
Annual risk of revisions > 12 months - Acclarent	2.5%	2.0%	3.0%

Variables used in multi-way scenario-based sensitivity analysis

The model is designed to be flexible to easily consider different scenarios and alternative assumptions. Alternative options can easily be considered by selecting a different options where there is a drop down list, denoted by an arrow. The model options include:

- **Comparator:** The model will default to considering XprESS compared to FESS, but the user can select to compare XprESS to Acclarent
- **Anaesthesia:** The model will default to assuming all surgeries are completed in theatre under general anaesthesia but the user can select to consider a scenario where a proportion of surgeries are done under local, where all surgical costs are expected to be proportionally lower
- **Outcomes Adjustment:** The model will default to using UK audit data for the revision transition probabilities (TPs) and applying a relative risk to estimate outcomes with BCDs. Alternatively, the user can select to apply the results from REMODEL directly and assume the rates with Acclarent are the same as XprESS
- **Time Horizon**: The model will default to a 5 year time horizon but the user can select to consider any time horizon between 1 and 5, in whole year increments
- **Discount Rate Costs:** The discount rate will default to 3.5% and will be applied to all costs beyond 1 year but the user can select to change this to any value between 0% and 100%
- **Source of estimate - procedure time***:* The selected source determines the procedure time for XprESS and the comparator. The options include outcomes reported by UK expert opinion or an Italian RCT
- **Source of estimate – length of stay:** The selected source determines the length of stay after XprESS and the comparator. All options were sourced from UK HES data (HSCIC) but differ by procedure type
- **Source– % under local:** The selected source determines the percentage of surgeries conducted under local anaesthesia where the options include expert opinion or USA data

Details of the alternative inputs applied for each scenario are described below

Surgical time options

Procedure time				
Option	**XprESS**	**FESS**	**Acclarent**	**Source / Assumption**
UK expert opinion	30 min	90 min	40 min	The base-case considers the procedure time for treating multiple sinuses and defaults to applying UK expert opinion. In the UK, when treating CRS patients multiple procedures are typically performed in one episode of care setting. As reported by the UK HES database, in some cases up to 7 individual procedures are performed within one episode of care and on an average, 2.75 procedures are performed per episode [HSCIC HES]. With FESS each procedure requires additional work, extending the time in theatre. Similarly with Acclarent, additional catheters are required when treating more than one sinus, which extends theatre time. In contrast, with the XprESS device multiple sinuses can be treated with the same catheter, hence minimal additional theatre time is required to advance and treat additional sinuses in the same episode of care. The estimated operative time based on feedback from UK physicians for an average episode of care with XprESS is 30 +/-5 minutes, with FESS is 90 +/- 15 minutes and with Acclarent is 40 +/-5 minutes. This estimate for FESS is consistent with procedures time of 42 minutes with FESS for unilateral reported in UK audits (Hopkins 2006), assuming that an average episode of care requires a bilateral approach and multiple sinuses treated (thus requiring considerably more time to perform both sides).
Italian RCT	32 min (same as Acclarent)	65 min	32 min	A scenario analysis consider the procedure time for treating only the fontal sinus, using the procedure times reported in a recent Italian RCT (Marzetti et al., 2014).

				This study captured procedure times with FESS and a BCD when treating a frontal sinus. Due to the work involved in treating the frontal sinuses, the time normally allotted to treat tends to be the longest. Here the procedure time with FESS was found to be 65 +/- 15 minute and with a BCD 32 +/- 15 min. The procedure times for treating a single sinus are assumed to be the same for both BCD technologies as no additional catheters are required. There is only expected to be a difference in procedure time between BCD technologies when more than one sinus is treated. However, even when treating a single sinus the procedure time is almost doubled with FESS compared to XprESS. This defences in procedure time is even greater when multiple sinuses are treated in one episode of care, as is the norm in the UK.

Length of hospital stay options

Average length of hospital stay				
Option	**XprESS**	**FESS**	**Acclarent**	**Source / Assumption**
E148 Frontal sinus	0.43	0.97	0.43	Recovery times with FESS and BCDs were obtained from three difference episodes of care codes. The code for E148 frontal sinus was applied in the base-case as the highest volume of BCD procedures were reported under this code. The other was considered in scenario analyses
E133 Intra. Antro.	0.27	0.60	0.27	

% of surgeries conducted under local options

% conducted under local			
XprESS	**FESS**	**Acclarent**	**Source / Assumption**
60%	2.1%	60%	The UK audit data reported that only 2.1% of FESS are done under local. Expert opinion anticipates that +60% of BCD procedures would move to local if XprESS was the recommended CRS surgical procedure
91.3%	1%	91.3%	Obtained from Medicare data on the proportion of sinus procedures conducted in an office setting with each technology

Variable values used in probabilistic sensitivity analysis

Not applicable.

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

Not applicable

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis.

Base-case results – XprESS compared to FESS

	Total per patient cost (£)
XprESS	2,679
FESS	3,981
Difference	1,302

Breakdown of costs per person - XprESS compared to FESS

Comparator	Surgery excluding. Equip	Equipment	GP visits 3 <months	Pain Mgt.	Admission 3 <months	GP visits beyond 3 months	Revisions	Total
	(£)	(£)	(£)	(£)	(£)	(£)	(£)	(£)
XprESS	984	900	42	0	14	511	228	2,679

FESS	2,594	300	74	0	25	590	397	3981
Difference	1,610	-600	32	0	11	80	169	1,302

Breakdown of costs overtime - XprESS compared to FESS

Year	XprESS (£)	FESS (£)	Annual Difference (£)	Cumulative Difference (£)
Year 1	2,095	3,212	1,117	1,117
Year 2	155	205	50	1,167
Year 3	149	196	47	1,215
Year 4	143	188	45	1,259
Year 5	137	179	42	1,302
TOTAL	2,679	3,981	1,302	

Base-case results – XprESS compared to Acclarent

	Total per patient cost (£)
XprESS	2,679
Acclarent	3,210
Difference	531

Breakdown of costs per person - XprESS compared to Acclarent

Comparator	Surgery excluding. Equip	Equipment	GP visits 3 <months	Pain Mgt.	Admission 3 <months	GP visits beyond 3 months	Revisions	Total
	(£)	(£)	(£)	(£)	(£)	(£)	(£)	(£)
XprESS	984	900	42	0	14	511	228	2,679
FESS	1,216	1,141	42	0	14	511	285	3,210
Difference	232	241	0	0	0	0	57	531

Breakdown of costs overtime - XprESS compared to Acclarent

Year	XprESS (£)	Acclarent (£)	Annual Difference (£)	Cumulative Difference (£)
Year 1	2,095	2,586	491	491
Year 2	155	166	11	502
Year 3	149	159	10	512
Year 4	143	153	10	522
Year 5	137	146	9	531
TOTAL	2,679	3,210	531	

9.5.2 Report the total difference in costs between the technology and comparator(s).

Compared to FESS, XprESS is estimated to result in savings of £1,302 per patients, mainly due to a reduction in the procedure costs. A breakdown of the cost per patient is reported above. This shows that the additional cost of XprESS equipment is easily offset by cost-savings from reduced surgical procedure costs, as well as other downstream cost-savings from GP visits, readmission and revisions avoided. The table showing the costs over time shows that the majority of the cost-savings are accumulated in the first year due to the difference in surgical procedure costs. There are also some further savings from reduced admissions, GP visits and revision risk.

Compared to Acclarent, XprESS is also estimated to results in cost savings. The tables above reports the total cost savings and a breakdown of total costs, by cost type. The total savings were estimated to be £531 per patients, mainly due to a reduction in the equipment cost. This suggest that most of the cost-savings are due to the differences in equipment costs and the surgical costs as the procedure is expected to be approximately 10 minutes shorter in the base-case where it is assumed 3 procedures are performed. While the rate of revision surgeries is expected to be the same for both procedures, XprESS is expected to result in cost-savings compared to Acclarent due to the lower cost of revision surgery with XprESS. The costs are not reported over time here as almost all the difference in costs is accumulated in the first year, apart from a small difference in revision costs. Similarly, no other difference in outcomes is reported as all outcomes are assumed to be the same with both XprESS and Acclarent.

9.5.3 Provide details of the costs for the technology and its comparator by category of cost.

All total costs for each comparator and the incremental costs are reported in section **9.5.1 above.**

Summary of costs by category of cost per patient

Item	**Cost *intervention (XprESS)***	**Cost *comparator (Acclarent)***	**Increment**	**Absolute increment**	**% absolute increment**
	Xtech	*Ytech*	*Xtech – Ytech*	*|Xtech – Ytech|*	*|Xtech – Ytech|/ (Total absolute increment)*
Surgery excluding. Equip	£984	£2594	£1610	£1610	100%
Equipment	£900	£300	-£600	-£600	100%
GP visits 3 <months	£42	£74	£32	£32	100%
Pain Mgt.	£0	£0	£0	£0	100%
Admission 3 <months	£14	£25	£11	£11	100%
GP visits beyond 3 months	£511	£590	£80	£80	100%
Revisions	£228	£397	£169	£169	100%
Total	£2679	£3981	£1302	£1302	100%
Item	**Cost intervention (XprESS)**	**Cost comparator (Acclarent)**	**Increment**	**Absolute increment**	**% absolute increment**
	Xtech	Ytech	Xtech – Ytech	|Xtech – Ytech|	|Xtech – Ytech|/ (Total absolute increment)

Surgery excluding. Equip	£984	£ 1,216	£232	£232	100%
Equipment	£900	£ 1,141	£241	£241	100%
GP visits 3 <months	£ 42	£ 42	£0	£0	100%
Pain Mgt.	£0	£ -	£0	£0	100%
Admission 3 <months	£14	£ 14	£0	£0	100%
GP visits beyond 3 months	£511	£ 511	£0	£0	100%
Revisions	£228	£ 285	£57	£57	100%
Total	£2,679	£ 3,210	531	531	100%

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state.

Not applicable

If appropriate, provide details of the costs for the technology and its comparator by adverse event.

Not applicable

Sensitivity analysis results

9.5.5 Present results of deterministic one-way sensitivity analysis of the variables.

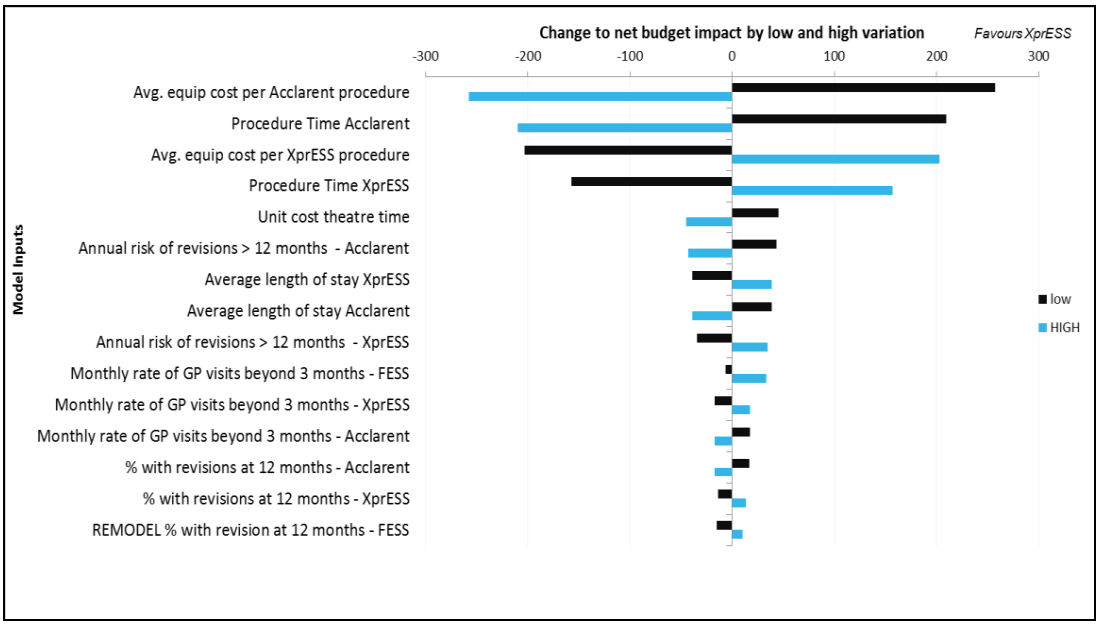
The results of the DSA comparing XprESS to FESS are illustrated below and the range of costs savings with XprESS found by the DSA are reported in the Table below.

These results show that varying the inputs for procedure time with FESS and unit cost theatre time have the largest and second largest impact on the net budget impact per patient result, respectively. Varying the input for procedure time with FESS by 20% varies the net budget impact per patient between £1,044 and £1,559. Varying any other inputs by 20% does not exceed this

range. This validates the conclusion that XprESS is very likely to result in cost-savings of at least £800 per patients and may be much higher.

	BASE-CASE £	LOWEST ESTIMATE £	HIGHEST ESTIMATE £
Range of cost-savings with XprESS compared to FESS	1302	1044	1559

Tornado plot of DSA reported for XprESS compared to FESS



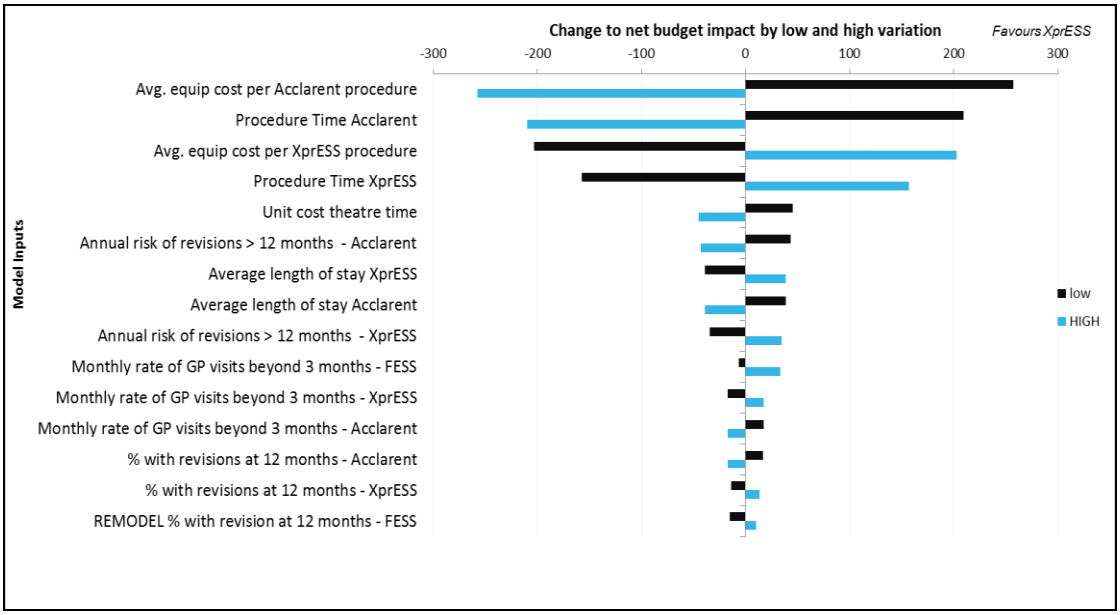
The results of the DSA comparing XprESS to Acclarent are illustrated below and the range of costs savings with XprESS found by the DSA are reported in the table below.

Unsurprisingly, varying the equipment cost for Acclarent and the procedure time with Acclarent have the greatest impact on the potential cost savings, as most other inputs are assumed to be equal for XprESS and Acclarent. Varying the equipment cost for Acclarent by 20% varies the net budget impact per patient between £274 and £784. No input varied by 20% resulted in a negative budget impact this therefore supports the conclusion that XprESS is very likely to be cost-savings compared to Acclarent.

Range of cost-savings reported in the DSA for XprESS compared to Acclarent

	BASE-CASE (£)	LOWEST ESTIMATE (£)	HIGHEST ESTIMATE (£)
Range of cost-savings with XprESS compared to Acclarent	531	274	784

Tornado plot of DSA reported for XprESS compared to Acclarent



9.5.6 Present results of deterministic multi-way scenario sensitivity analysis.

The table below reports the cumulative cost-savings with XprESS compared to both technologies over different model time horizons. In both cases, the cost-savings increase with longer time horizons, due to lower costs for GP visits and revisions with XprESS compared to FESS and Acclarent. Neither comparisons are particularly sensitive to the time horizon as in both scenarios most of the costs occur in year 1.

Time Horizon	XprESS vs. FESS	XprESS vs. Acclarent
	(£)	(£)
1 year	1,117	491
2 year	1,167	502
3 year	1,215	512
4 year	1,259	522
5 year (Base)	1,302	531

The next table reports the cost-savings per patients with XprESS compared to both technologies when alternative options from the base-case default settings are selected. The following observations can be made from these results:

- When the option to include anaesthesia is selected the cost-savings are even greater with XprESS compared to FESS. This is because if conducting surgeries under local was a recommended pathway, most BCD surgeries are expected to be done under local, while most FESS procedures would still need to be conducted under general in theatre. Changing this option has minimal impact of the results for XprESS compared to Acclarent
- Applying the REMODEL results directly, slightly decreases the cost-savings with XprESS compared to both comparators. This is because accounting for the higher UK base-line rates inflates any cost savings with XprESS, as XprESS is associated with lower revision rates and less costly revision surgeries
- Applying the results of the Italian RCT reduces costs savings with XprESS for both technologies but still supports the conclusions that XprESS is cost-saving. This scenario is expected to reflect the lowest difference in procedure time compared to both technologies as this study only captures the difference in surgery time when treating a frontal sinus. In reality the difference in procedure time is expected to be much higher when multiple sinuses are treating in one episode, as is common practice in the NHS.
- Varying the source of the time to discharge inputs changes the estimated cost-savings with XprESS compared to FESS but did not impact the conclusion that XprESS was cost-saving. This is because the difference in time to discharge was relatively consistent under all procedure codes. In all procedure codes the time to discharge was shorter with a BCD plus FESS compared to FESS.
- Changing the source of the % of procedures conducted under local anaesthesia and applying the rates reported in the USA increases the

potential cost-savings with XprESS compared to FESS. This is because a conservative assumption was applied in the base-case as this practice is not common in the UK. This suggests that the cost-savings may be even higher if there is a shift to conduct most XprESS surgeries under local, similar to trends in the USA.

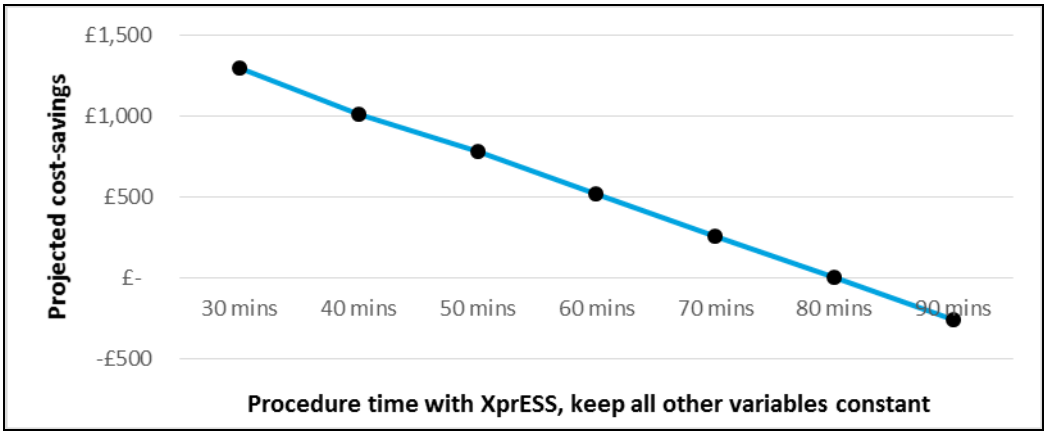
- Changing the unit cost of theatre time to a low estimate decreases the potential cost-savings associated with XprESS considerably, however even applying this very low estimate XprESS results in cost-savings compared to FESS. The low estimate applied was obtained from a Hernia costing study where the theatre costs are expected to be lower than for CRS surgery. In reality, the cost of theatre time is expected to vary widely by hospital and by procedure type and is likely to be close to the base-case for most hospitals.

OPTION	DEFAULT	RESULTS UNDER ALTERNATIVE OPTION		
		Option	XprESS vs. FESS	XprESS vs. Acclarent
			(£)	(£)
Base	All defaults	NA	1,302	531
Anaesthesia	General only	Include local	1,520	470
Outcomes Adjustment	UK Adjustment	REMODEL unadjusted.	1,222	504
Source of estimate - procedure time	UK Experts	Italian RCT	550	257
Source of estimate - length of hospital stay	E148 frontal sinus	E133 Intra. Antro.	1,205	531
Source of estimate - % under local	UK expert opinion	USA data	1,302	531
Unit cost theatre time (per min)	Average surgery	Low cost surgery	367	352

The first graph below illustrates the results of a breakeven analysis whereby the input for the procedure time with XprESS was varied while keeping all other inputs constant. Applying the goal seek function in excel found that XprESS was cost-neutral with a procedure time of 80 minutes and was more expensive at procedure times above this. As all estimates reported by UK experts, the Italian study and CMS databases consistently reported the procedure time with XprESS as lower than 80 minutes, this break-even

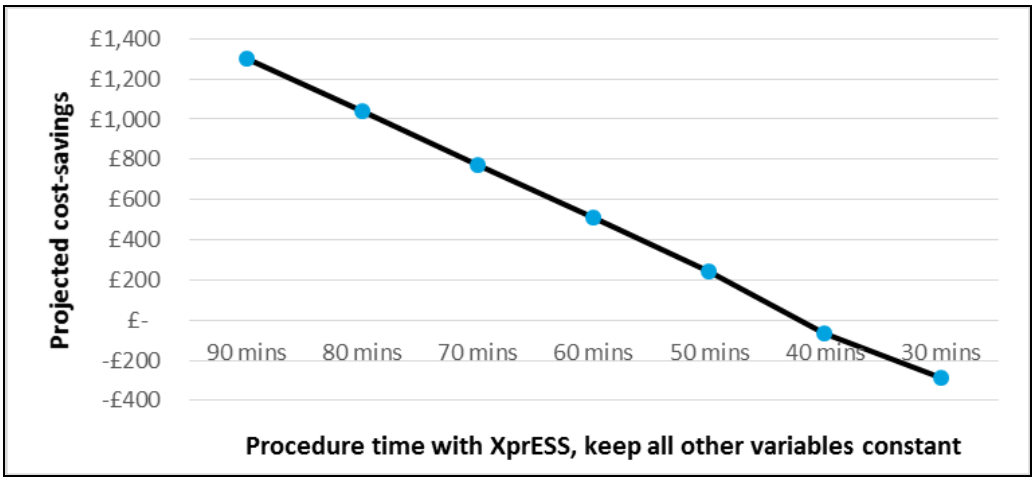
analysis validates the conclusions that XprESS is expected to be cost-savings compared to FESS.

Breakeven analysis varying procedure time with XprESS



As there could be a possible difference around the specific procedure time with FESS, this input was also varied to demonstration a breakeven analysis and the results are presented below. This displays that XprESS is cost neutral or cost-savings for any procedure time with FESS above 41 minutes. This is much lower than the estimates provided by our clinical experts of 90 +/- 15 minutes. This therefore also validates the conclusion that XprESS is likely to result in cost-savings.

Breakeven analysis varying procedure time with FESS



9.5.7 Present results of the probabilistic sensitivity analysis described in table C10.3.

Not applicable

9.5.8 What were the main findings of each of the sensitivity analyses?

This is detailed in 10.3.6 and 10.3.7 above 8.1.1

9.5.10 what are the key drivers of the cost results?

The main drives for the results in the analysis comparing XprESS to FESS include:

- The procedure time
- The cost of the equipment
- The length of hospital stay, and
- The cost of theatre time

The main drivers for the results in the analysis comparing XprESS to Acclarent are the equipment costs and the length of procedure time

9.5.11 Miscellaneous results

Not applicable

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

Not applicable

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

Not applicable

9.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable

9.6.3 Describe how the subgroups were included in the cost analysis.

Not applicable

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

Not applicable

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The results of the model were validated internally by calculating the cost in the first year in two ways. The cost were first calculated on a decision tree (in the decision tree sheet of the model), then they were also calculated by cost type in a breakdown of cost type. This is also in the decision sheet of the model.

All model calculations were calculated by a primary health economist and cross checked and internally validated by a second modeller.

The results could not be validated by any published models as no prior models were identified in the systematic literature review, however the results are consistent with preliminary cost analysis submit to NICE via the notification document for XprESS.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results of this de novo analysis show that XprESS results in cost-savings of approximately £1300 per patient compared to FESS, when treating average risk patients for CRS surgery where multiple sinuses are treated in one episode of care. Most of these cost-savings are due to reduced time in theatre and faster recovery but also include cost-savings from reduced healthcare utilisation and fewer surgical revisions.

This results is consistence with budget impact models comparing BCD with FESS. (Holy et al., 2013)

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes. The costs are not expected to differ by subgroup therefore the cost of this analysis are relevant to all subgroups in which XprESS has an indication.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The strength of this de novo economic analysis include the model structure, the applicability to UK decision makers and the robustness of the scenario analysis, as detailed below:

- The model structure has been designed to capture all relevant costs and outcomes. In addition to the costs incurred in hospital the model also considered all short and medium-term resource utilisation. This enables decision-maker to consider the full impact of switching form FESS to XprESS on all healthcare utilisation.
- All inputs and assumptions have been selected to reflect resource utilisation from an NHS payer perspective. The resource utilisation in the standard care (FESS) arm were mainly obtained from follow-up of the 2003 UK audit of CRS surgeries and the outcomes for XprESS were estimated applied relative differences obtained from a large RCT. As such, the results are expected to reflect cost-savings if XprESS was rolled out widely in England.

An additional advantage of the model structure is the flexibility to consider alternative sources for all key model assumptions. This has facilitated extensive scenario analysis to validate the model results

The conclusions of this analysis are expected to be robust as they have been tested against sensitivity analysis and consider multiple scenarios. Nonetheless, there may be several possible limitations that should be considered which are listed below:

- There is limited published research on the procedure times for conducting multiple procedures with each intervention. The base-case

results were obtained from estimates provided by UK clinicians and are expected to reflect real-world outcomes in the UK. Given the uncertainty around these inputs, these were tested in a break-even analyses which showed that all plausible estimates supported the conclusion that XprESS is cost-saving compared to FESS.

- There may be uncertainty regarding the relative difference in outcomes between XprESS and FESS beyond two years as this was the duration of the main RCT applied in the model. The model assumes that the relative difference between XprESS and FESS is constant beyond 12 months. This assumption is well justified on the grounds that clinical studies show symptom improvement remains stable from as early as 1 week post standalone balloon procedure out to 2 years. Similarly, improvement in QOL scores after FESS does not appear to change between 6 months and 20 months. As such, it is reasonable that any difference in XprESS compared to FESS at 12 months is expected to be constant over time.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The results of this analysis should be updated when more UK–specific data on the procedure times for XprESS is available and the proportion of procedures conducted under local anaesthesia. In this analysis conservative assumptions for these inputs were applied but it is expected that the cost-savings compared to FESS may be even higher.

9.9 References:

Includes for both sections B and C, clinical and economic and the technical document in Attachment 1 of this submission:

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Attachments

The following attachments are provided in a separate document.

Attachment 1: Technical Document for the XprESS Cost Model

Attachment 2: The XprESS Multi-Sinus Dilation System Cost Model

Attachment 3: Coding and HSCIC Data prepared by Device Access June 16, 2015

Attachment 4: PDF copies of the selected articles

10. Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information was provided in detail in section 7.1.1

10.2 The specific databases searched and the service provider used

10.2.1 The date on which the search was conducted.

10.2.2 The date span of the search.

10.2.3 The complete search strategies used, including all the search terms:

Search databases: Medline (via OVID), Medline (via Pubmed), Embase (via OVID), Cochrane Database of Systematic Reviews (via Wiley)
Search date: December 29, 2015
Search date span: 2006 to December 29, 2015
Inclusion criteria: English language, Human studies
Exclusion criteria: case reports, editorials, letters, review articles, books, technology assessment reviews, modeling/bench/non-human studies, false hits
Search strategies:

Terms	Results
Medline (via OVID)	
exp Sinusitis OR (sinusitis OR rhinosinusitis).af	22,373
exp Dilatation, Pathologic OR ((dilat* or balloon* or catheter* or sinuplast*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier])	415,977
Sinusitis terms AND dilatation terms	392
Limits: English, Human, 2006 to present	**160**
Embase (via OVID)	
exp sinusitis OR exp rhinosinusitis	37,053
exp balloon catheter/ OR exp balloon dilatation/ OR ((dilat* or balloon* or catheter*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]) OR (sinuplast*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword])	593,554
Sinusitis terms AND dilatation terms	778
Limits: English, Human, 2006 to present, remove Medline	**58**
Medline (via Pubmed)	
("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*) AND ("Sinusitis"[Mesh] OR sinusitis OR rhinosinusitis OR sinuplast*) AND (Limits: English, Human, 2006-present)	**172**

10.2.4 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Not applicable

10.2.5 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Patients with chronic rhinosinusitis
Interventions	Balloon sinus dilation using the XprESS Multi-Sinus Dilation System or equivalent. Functional endoscopic sinus surgery (FESS) (comparator intervention)
Outcomes	Technical success, sinus symptom improvement, debridement rate, revision surgery rate, recovery outcomes, healthcare utilization, work productivity, ostial patency rate, procedure pain, and complications.
Study design	Meta-analysis, randomized controlled trial, observational case series, comparative case series, retrospective chart reviews, case reports
Language restrictions	English
Search dates	2006 to present
Exclusion criteria	
Population	Patients with conditions other than chronic rhinosinusitis, cadaver studies, non-human studies
Interventions	Balloon sinus dilation with products other than the XprESS and FinESS devices or unspecified balloon dilation devices Off-label uses of the XprESS or FinESS devices Sinus procedures not involving balloon technology
Outcomes	Outcomes not related to the efficacy or safety of balloon sinus dilation (incidental use of balloon dilation in a study with an unrelated objective)
Study design	Insurance claims database analyses, technology assessments, medical policy statements, reviews, commentary, letter to the editors
Language restrictions	Non-English
Search dates	Before 2006

10.2.6 The data abstraction strategy.

Not applicable

10.3 *Appendix 2: Search strategy for adverse events (section 7.7.1)*

The following information should be provided.

10.3.1 The specific databases searched and the service provider used

All of the articles selected and summarized in section 7.3 assessed complications or adverse events as a study outcome. None of the studies were statistically powered for the detection of safety event rates. The reporting of adverse events varied across studies with some reporting all serious and non-serious events while others reported only device- and procedure-related adverse events. Despite this variability in reporting, it is clear that serious adverse events related to the balloon device or procedure are very rare.

10.3.2 The date on which the search was conducted.

Not applicable

10.3.3 The date span of the search.

Not applicable

10.3.4 The complete search strategies used, including all the search terms:

Not applicable

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

10.3.6 The inclusion and exclusion criteria.

Not applicable

10.3.7 The data abstraction strategy.

Not applicable

10.4 *Appendix 3: Search strategy for economic evidence (section 8.1.1)*

The detailed information of the search was provided in 8.1.

10.4.1 The specific databases searched and the service provider used

Databases Searched: Medline (via OVID), Medline (via Pubmed), Embase (via OVID), Cochrane Database of Systematic Reviews (via Wiley), NHS EED* (via University of York, Center for Reviews & Dissemination (CRD) website).

* NIHR funding to produce DARE and NHS EED ceased at the end of March 2015. However, both databases can still be accessed via the CRD website. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014. Bibliographic records were published on DARE and NHS EED until 31st March 2015. The HTA database will continue to be produced by CRD for the foreseeable future.

10.4.2 The date on which the search was conducted.

February 22, 2016

10.4.3 The date span of the search.

2010 to February 22, 2016

10.4.4 The complete search strategies used, including all the search terms:

Search Strategy:

Medline (via OVID)

Terms	Results
exp Sinusitis/ or (sinusitis or rhinosinusitis or rhino-sinusitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	22,177
exp dilatation, pathologic/ or (dilat* or balloon* or catheter*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	411,168

sinuplast*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	61
(Sinusitis terms AND dilatation terms) OR sinuplasty	405
exp models, economic/ or cost.mp. or costs.mp. or economic*.mp. or cost-analysis.mp. or exp economics/ or insurance.mp. or exp insurance/ or reimburs*.mp. or claim.mp. or claims.mp. or charge*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	987,449
Sinusitis dilation terms AND economic terms	**20**
Limits: English, 2010 to present	**13**

Embase (via OVID)

Terms	**Results**
exp sinusitis OR exp rhinosinusitis	37453
exp balloon catheter/ or exp ballooon dilatation/ or (dilat* or balloon* or catheter*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	600785
sinuplast*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	117
(Sinusitis terms AND dilatation terms) OR sinuplasty	823
(model or models or modeling or modelling or cost or costs or cost-analysis or economic* or insurance* or reimburs* or claim or claims or charge*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4549647
Sinusitis dilation terms AND economic terms; Limits: English, 2010 to present	**89**

Medline (via Pubmed)

Terms	**Results**
Search (((((("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*))) AND (("Sinusitis"[Mesh] OR sinusitis OR rhino-sinusitis OR rhinosinusitis)))) OR sinuplast*)) AND (models, economic [mh] OR "costs and cost analysis" [mh] OR economics [mh] OR insurance [mh] OR model or models or modeling or modelling or cost or costs or cost-analysis or economic* or insurance* or reimburs* or claim or claims or charge*) Sort by: PublicationDate Filters: Publication date from 2010/01/01 to 2016/12/31; English	**22**

NHS EED (via CRD website): Total references: **10**

10.4.5 Details of any additional searches

Not applicable

10.5 *Appendix 4: Resource identification, measurement and valuation (section 9.3.2)*

The following information should be provided.

10.5.1 The specific databases searched and the service provider used

Not applicable

10.5.2 The date on which the search was conducted.

Not applicable

10.5.3 The date span of the search.

Not applicable

10.5.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable

10.5.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

10.5.6 The inclusion and exclusion criteria.

Not applicable

10.5.7 The data abstraction strategy.

Not applicable

11. Related procedures for evidence submission

11.1 *Cost models*

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.1 *Disclosure of information*

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.2 *Equality*

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

11.31 Describe equality issues related to patient population and condition

None are known at this time.

11.32 Describe equality issues related to the assessment of the technology

None are known at this time.

11.33 How will the submission address these issues?

The submission does not address equality since there are no known equality issues associated with the patient population, condition, technology, or procedure

XprESS Multi-Sinus Dilation System (MSDS) for the Treatment of Chronic Rhinosinusitis

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Model Technical Document

Version 1.0

08 March 2015

Margaret Boiano-Entellus Medical
Deirdre Blissett-Device Access

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Glossary

BCD: Balloon Catheter Device
CCA: Cost Consequence Analysis
CRS: Chronic Rhinosinusitis
FESS: Functional Endoscopic Sinus Surgery
HES: Hospital Episode Statistics
HRQoL: Health Related Quality of Life
MSDS: Multi-Sinus Dilation System
NHIS: National Health Interview Survey
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
RR: Relative Risk
RCT: Randomised Controlled Trial
SLR: Systematic Literature Review
TP: Transition Probability

1 Background and Objectives

This section provides relevant background information including an overview of Chronic Rhinosinusitis (CRS), a description of the XprESS Multi-Sinus Dilation System (MSDS), a description the current treatment pathways in the English National Health Services (NHS) and the rationale for this analysis.

1.1 Overview of Chronic Rhinosinusitis (CRS)

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses. It is sub-categorised depending on the persistence and recurrence of symptoms. Where symptoms are resolved within twelve weeks of onset this is referred to as acute rhinosinusitis but where symptoms persist beyond twelve weeks this is referred to as chronic rhinosinusitis (CRS)(ENT-UK, 2013). CRS also includes recurrent acute rhinosinusitis in which symptoms reoccur four or more times in one year (Rosenfeld et al., 2015).

CRS is not usually a life-treating condition but moderate to severe CRS has a detrimental impact on patients' health related quality of life (HRQoL). The symptoms of CRS include chronic nasal congestion, facial pressure and pain, headache, hyposmia, and anosmia. HRQoL amongst patients with CRS is typically measured using the SNOT-22 score, a 22-item outcome measure applicable to sino-nasal conditions. This measure derives a score ranging between 0 and 110 on a SNOT-22 scale, where higher scores imply greater impact on HRQoL (Rudmik and Smith, 2011).

CRS also represents a significant cost-burden to the National Health Service (NHS) and wider society. CRS is a relatively common condition, estimated to affect 11% of the UK population (Hastan et al., 2011) and sufferers of CRS are frequently off work and on prescribed medication to treated CRS episodes. A burden of illness study conducted in the USA estimated that for an affected individual CRS accounted for 4.8 to 5.7 days of missed work per year, compared to 3.74 days of missed work per year for individuals that were not affected by CRS. This was estimated to have an overall yearly economic cost of $1,539 per patient (Bhattacharyya, 2003).

Surgical treatment for CRS has been shown to reduce symptoms and significantly improve HRQoL and healthcare resource utilisation. Published data of HRQoL following CRS surgery with a Balloon Catheter Device (BCD) (Chandra et al., 2016, Stankiewicz et al., 2012, Weiss et al., 2008) show symptom improvement remains stable from as early as 1 week post standalone balloon procedure out to 2 years. Similarly, two year follow up of CRS surgery with FESS or BCDs found a reduction in healthcare utilisation post-surgery with both types of surgery and that this reduction in CRS episodes stabilized between 6 and 18 months (Chandra et al., 2016). Similar findings are reported in other studies (Soler and Smith, 2010), noting improvement in HRQoL scores after FESS does not appear to change between 6 months and 20 months. Therefore, assessment of HRQoL at 6 months has been established as an acceptable long-term primary endpoint for use in rhinosinusitis clinical trials.

1.2 Treatment pathway

Progressive medical management is the fist-line treatment option recommended for CRS. Medical treatment regimens include antibiotics and anti-inflammatory medications (corticosteroids). Due to frequently recurring sinus infections many patients undergo multiple regimens of antibiotic therapy, often starting with amoxicillin or Augmentin and then progressing to cephalosporins, macrolides, and/or quinolone antibiotic therapy. Since medical therapy does not address the underlying anatomical issues contributing to the disease, medical treatment alone does not satisfactorily resolve all symptoms for some patients.

British guidelines recommend surgery as a second-line treatment option for CRS(Fokkens et al., 2012). When CRS symptoms persist or recur frequently despite ongoing or progressive medical management, patients are usually referred for functional endoscopic sinus surgery (FESS).

Barriers to Access

There is currently an undersupply of CRS surgeries in England and access to CRS surgery varies widely by region. Analysis of HES activity in 2014 found that approximately 213,000 UK patients per year are referred to sinus surgery (FESS) annually, yet only approximately 32,500 FESS procedures are completed annually (HSCIC). The same analysis found that in March 2014, 2,432 patients in England waited longer than 18 weeks for ENT Surgery, suggesting that it is relatively common for providers to incur waiting list fines. Access to CRS surgery is also reported to vary regionally, with a recent NHS commissioning report finding a five-fold variation in procedure rates for sinus surgery per 100,000 population by CCG across England (ENT-UK, 2013).

Barriers to access and long waiting time has important economic implications as delaying surgery is associated with higher healthcare utilisation. A recent UK study compared outcomes amongst patients accessing treatment early, defined as within 12 months of CRS diagnosis, with those accessing treatment late, defined as > 12 months after CRS diagnosis. This study found that the cohort accessing treatment late used significantly more CRS-related care measured in terms of GP visits and prescription medication, compared to those accessing surgery early. (Hopkins et al., 2015) Similar conclusions were drawn from a USA study which observed gradual increases in health care utilisation across six groups stratified by the time interval between first sinusitis diagnoses to surgery with FESS (Benninger et al., 2015). If waiting lists are a contributing reason for delayed access, increasing the efficiency of the treatment pathway may allow more patients to be treated earlier reducing downstream NHS costs.

1.3 Surgical treatment of CRS in the NHS

FESS is considered the standard surgical option for CRS surgery as this accounts for the majority of surgeries in England. More recently BCDs entered this market as an alternative treatment option. The clinical practice and pathway of care is similar to that of FESS in that the CRS patient who has failed maximum medical management are referred to the specialist community/ENT Consultant surgeon to perform the procedure on the appropriate sinus (es).

The therapeutic intent of both FESS and balloon dilation is to improve patient quality of life through relief of persistent symptoms by enlarging the natural drainage pathways (ostia) of the affected sinuses to restore mucus flow and ventilation.

A description of each technology is detailed below.

Functional endoscopic sinus surgery (FESS)

FESS or ESS is a surgical treatment where physicians access the sinus ostia through the nose under endoscopic guidance. The procedure involves the use of rigid steel instruments and powered cutting tools such as microdebriders to remove inflamed sinus tissue and underlying bone to create a larger passage for restoring normal sinus drainage. Results of the FESS procedure includes irreversible changes to the anatomy, significant postoperative pain and discomfort and recovery time. Approximately 13% to 18% of UK FESS patients require revision surgery, often as a result of ongoing inflammation and scarring associated with the procedure (Philpott et al., 2015).

As FESS involves cutting and removing sinus tissue and bone it is almost always performed in an operating theatre with the patient under general anaesthesia. Although FESS is designed to preserve the mucosa and cilia lining of the sinuses as much as possible, it remains an invasive procedure. After FESS, patients usually return to normal daily activities within 7 to 14 days. Additional office visits and debridement procedures are often required after FESS to ensure appropriate healing occurs.

Balloon Catheter Device (BCD)

In contrast to FESS, when balloon sinus dilation is performed the bony sinus outflow tracts are remodeled by balloon displacement of adjacent bone and paranasal sinus structures, which allows sustained remodeling and enlargement of the sinus drainage path when the bone heals in the dilated state. The procedure is minimally invasive with patients typically returning to normal daily activities within 1 to 2 days.

Since no tissue is removed and mucosa is preserved, BCD is a far less invasive procedure compared to FESS and can offers many advantages including being a faster procedure to perform, quicker recovery and fewer short and medium term adverse events. Debridement procedures are rarely required and patients require postoperative prescription pain medications for shorter durations than those who undergo FESS.

A further significant advantage of surgeries with BCD over FESS is the opportunity to conduct procedures under local anesthesia in less resource intensive settings. As surgical procedures under local anaesthesia require less preparation, fewer staff and can be conducted in an ambulatory settings, the unit cost of theatre time is expected to be considerably lower. In the USA, based on the Center for Medicare & Medicaid Services (CMS) 2014 claims data over 90% of BCD procedures are done under local in an office setting. The CMS data is provided in **Appendix 4**.

BCDs can be considered as both a direct replacement for FESS when used to conduct the full procedure (referred to as standalone BCD), or as adjunct device in addition to traditional endoscopic cutting instruments when used in combination with FESS (referred to as a hybrid procedure).

When using in a hybrid procedure the balloon allows the ENT surgeon to be less invasive and preserve more anatomy. Dissection is used to remove the diseased bone and tissue within the sinuses. Utilizing the balloon helps create a pathway or helps enlarge the ostium. As a results is less local trauma and this reduces the invasiveness of the intervention as well as reducing the blood loss and preserving more mucosal vs. traditional FESS.

Acclarent

The Acclarent Balloon Catheter Device (BCD) was the first BCD available in the UK and was generally used to perform hybrid balloon dilation procedures with FESS, however, as of Dec 31st 2015 it is no longer distributed in England.

Early studies of the Acclarent device indicated many cases have been hybrid procedures making it difficult to evaluate the contribution made by the technology as a standalone procedure. Experience as one of the first National Health Service hospitals to offer the procedure in the UK concluded that Acclarent offered many advantages, including the opportunity to conduct surgeries under local. Nevertheless there were concerns over its additional costs and that must be considered (Hopkins et al., 2011).

As such, the number of Acclarent BCD procedures performed in the NHS has had low utilization. Analysis of HES data in 2014 found that 13,010 FESS (Y761) procedures were conducted while only 259 FESS (Y761 and Y40.3) with balloon dilation procedures were performed.

XprESS

The XprESS Multi-Sinus Dilation System is a sterile, single-use system for treating chronic rhinosinusitis. The system comprises a balloon-tipped device with a reshapable end that is inserted through the nose into the maxillary, frontal, or sphenoid sinuses. The XprESS system also includes an inflation syringe, bending tool, and 2 extension lines to provide irrigation. The balloon is manipulated into the bony sinus outflow tracts (ostia) and inflated with saline to dilate and remodel them by displacing adjacent bone and paranasal sinus structures. This allows the sinuses to drain more effectively.

The XprESS system is expected to be used as a standalone procedure and to be sufficient to treat the majority of uncomplicated CRS surgeries in the UK especially when utilized earlier in the treatment pathway, just after maximal medical therapy has failed. When standalone balloon dilation procedures are performed with the XprESS Multi-Sinus Dilation System on the maxillary, frontal or sphenoid sinus ostia, they will replace the corresponding FESS procedure for the particular sinus (es).

The XprESS system has lately been launched in the UK as a direct comparator for FESS and Acclarent and is the intervention considered in this analysis. This analysis will focus only on utilizing the XprESS system to perform standalone balloon dilation of the sinus ostia, as this, is its primary indication and its safety and efficiency has been proven in a high quality, sufficiently powered, randomized controlled trial.

1.4 Objectives of this analysis

This cost consequence analysis (CCA) aims to estimate the cumulative difference in costs and consequence per patient undergoing surgery for CRS, comparing surgery with standalone XprESS BCD (hereby referred to as XprESS) to surgery with FESS or standalone Acclarent BCD for (herby referred to as Acclarent) in average risk patients attending for CRS surgery in England.

This de novo economic analysis was conducted to support a submission to the National Institute of Health and Clinical Excellence (NICE) Medical Technology Evaluation Programme (MTEP) process as no other economic evaluations were identified comparing XprESS to FESS or Acclarent from an NHS England perspective. As such, all cost and outcomes are considered from a NHS England perspective.

The use of XprESS as a hybrid device is not considered in this analysis as detailed above. Furthermore the indication for use of hybrid is subjective to the surgeon's judgement thus there is too much uncertainty around the indication.

2 Methodology

This section provides an overview of the methodology applied. This describes the population, the value arguments, the model structure and other key aspects of the model, including the model selection options.

2.1 Population

The base-case analysis considers an average risk patient attending for CRS surgery, where multiple sinuses are treated in one NHS episode of care. The HES databases for NHS England reports that a surgical intervention for CRS may include up to 7 procedures, with an on average episode of care comprising of 2.75 procedures (HSCIC). The base-case scenario will therefore consider a surgery involving multiple procedures (treating both sides) in one episode of care.

Sub-groups are not be explicitly analysed in the model as the clinical and economic benefits of XprESS relative to both comparators are relevant for all subgroups. There may be differences in procedure times and length of stay across subgroups, but the relative difference between XprESS and its comparators is expected to be similar. The findings of this analysis are therefore assumed to be relevant to all sub-groups where XprESS has an indication, including:

- Patients with uncomplicated chronic rhinosinusitis (or uncomplicated recurrent acute rhinosinusitis)
- Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis), with orbital or intracranial involvement
- Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) with and without nasal polyps
- Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) affecting the anterior ethmoid sinus in addition to maxillary, frontal or sphenoid sinus disease
- Patients with anatomic variants such as septal deviations and accessory ostia
- Children and young people under 18 years of age the outcomes are not expected to vary by subgroups.

2.2 Comparators and value arguments

As detailed above, the primary analysis will compare XprESS to FESS, the current standard of care in England. A secondary analysis will also compare XprESS to Acclarent, but the findings of this analysis are less relevant to NHS decision makers as this device is no longer distributed in the UK.

Compared to FESS

The following cost-saving attributes are considered in the analysis comparing XprESS to FESS, where surgery with XprESS is expected to results in:

- **Shorter theatre times** resulting in cost-savings from reduced surgical resources; this cost-saving alone is expected to off-set any additional equipment costs
- **Shorter recovery time** resulting in cost-savings due to faster hospital discharge
- **Improved patients comfort** resulting in cost-savings from reduced pain medication
- **Lower risk of post-surgery nasal bleeds** resulting in cost-savings from reduced GP visits, CRS medication and readmissions within 3 months of surgery
- **Lower risk of future CRS events** resulting in costs from reduced GP visits, CRS medication and surgery revision

The potential for further cost-savings by conducting a large proportion of XprESS surgeries under local anaesthesia are not included in the base-case but are considered in a scenario analysis. Currently most CRS surgeries are conducted in an operating theatre under general anaesthesia, thus the base-case applies a conservative assumption that XprESS replaces FESS as the standard device used in theatre and that all surgeries are continued to be conducted in theatre under general anaesthesia. This is a conservative assumption as it is expected that if this was recommended in guidelines more than half of CRS surgeries with XprESS would be performed under local when surgeons become familiar experienced in using XprESS. As surgical procedures under local anaesthesia require less preparation, fewer staff and can be conducted in an ambulatory settings the unit cost of theatre time is expected to be considerably lower. As ambulatory surgical facilities are already available and usually underutilised in the most NHS hospitals this switch in surgical location is not expected to require significant service redesign.

In addition to the cost-saving benefits, other benefit to the NHS and patient also captured in this analysis comparing XprESS to FESS include:

- **Fewer adverse events** requiring GP or hospital treatment within 3-months of surgery
- **Similar or lower** risk of **revision surgery**
- **Similar or improved HRQoL** compared to FESS, captured through reduced SNOT-20 scores

Compared to Acclarent

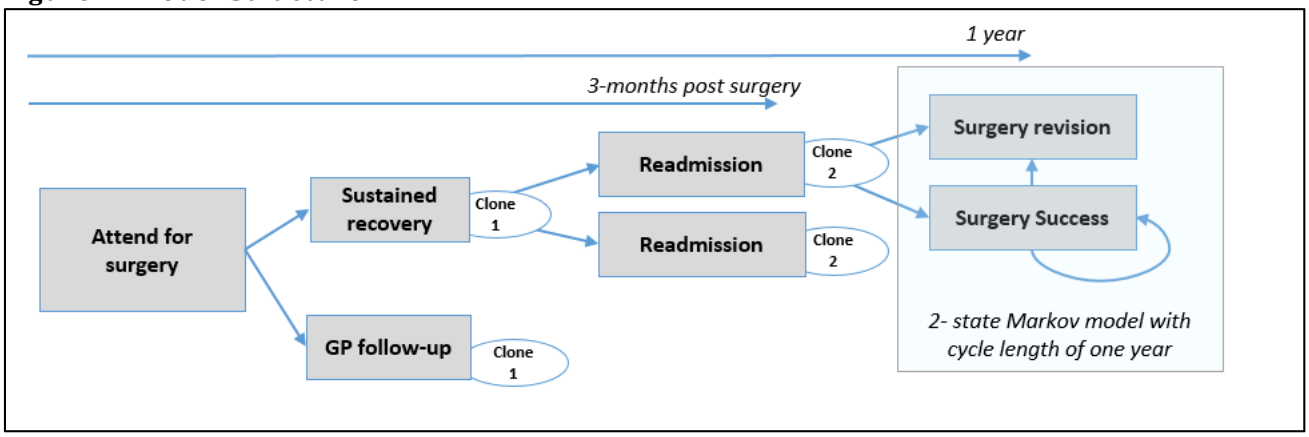
The same model is also used to capture differences in costs between CRS surgery with XprESS compared to Acclarent. As no head-to-head trials of XprESS compared to Acclarent are available, all outcomes are assumed to be the same for both BCDs. This analysis is thus limited to considering the following cost-saving advantaged:

- Compared to Acclarent, XprESS results in **shorter theatre times when treating multiple sinuses** as fewer components are required to advance and treat multiple sinuses
- As **fewer consumable** are used with XprESS procedure this is also expected to result in direct cost-savings from **reduced equipment costs**

2.3 Model structure

All differences in costs and outcomes are captured in an economic model. The model structure is based on a published budgeted Impact model structure comparing BCDs with FESS (Holy et al., 2013) and comprises of a decision tree followed by a two state Markov model. The decision tree captures costs and outcome in the first year and the Markov structure captures costs and outcomes between years 2 and 5, applying a one year cycle length. The model structure is illustrated in **Figure 1 below,** along with a description of how a cohort moves through the model.

Figure 1: Model Structure



A cohort of patients progress through the model as follows:

1. Patients enter the model having a CRS surgery for one of the indications specified for XprESS in 2.1 above. Costs in the initial health state are considered up to the point of discharge
2. Within the first three months post-discharge patients could have a sustained recovery or require one of more GP visits
3. Within the first 3 months patients are also at risk of readmission. This risk is assumed to be independent of if they require a GP visit
4. Beyond 3 months patients may transition to one of two mutually exclusive Markov health states, where they have a surgery revision or sustain recovery. Surgery revision is an absorbent health states as it is assumed that patients can only have one revision surgery
5. Irrespective of if patients have a revision surgery, all patients continue to be at risk of CRS episodes, albeit at a much lower rate than before surgery.

Mortality is not considered in the model as the model time horizon is a maximum of 5 years and CRS-related mortality is very rare and not expected to differ by intervention.

2.4 Key Aspects

Time horizon

The model time horizon is 5 years but most of the differences in cost are expected to accumulate in year 1. This time horizon was selected as this captures the medium-term differences in cost and outcomes. Costs were not captured beyond 5 years as audit data of patients with CRS surgery was only available for 5 years and there was too much uncertainty regarding the outcomes beyond this point 5 years.

Discounting

All costs beyond one year are discounted at a rate of 3.5% in accordance with NICE guideline for economic evaluation. No outcomes beyond 1 year are reported.

3 Model Inputs

This section describes the costs, outcomes, the base-line risk adjustment, the model selection options and a description of the model default inputs for each health state.

3.1 Costs

The costs considered in this analysis are limited to the costs incurred by the English NHS. Cost incurred by patients, carers, or society are not considered. Similarly, hospital fines, deficits or surpluses due to either waiting lists or readmissions or are outside the scope of this analysis.

The costs considered included:

- Hospital resources to conduct the procedure and manage recovery up until discharge, including equipment costs
- NHS resources to manage further treatment in the three months post-discharge, including prescription pain medication, GP visits and hospital readmissions
- NHS resources to manage repeat CRS episodes and surgery revisions

3.2 Outcomes

The outcomes reported included:

- Change in surgery time
- % requiring GP visits at 3 months, % requiring readmission and surgical revisions in the first year
- Change in SNOT-Score at 12 months

3.3 Model Sources

Selection of Clinical inputs and base-line adjustment

Specific searches were not carried out to source clinical inputs, instead all clinical inputs were selected by Entellus in consultation with internal and external clinical experts. The sources selected included a combination of real-world studies of post-surgical outcomes amongst English patients and randomised controlled trials (RCTs) identified in the systematic literature review (SLR) conducted alongside this analysis.

As patients in the UK typically access surgery later which is associated with worse outcomes (Hopkins et al., 2015, Benninger et al., 2015), the baseline risk of requiring healthcare utilisation or revision surgery is expected to be higher than outcomes reported in RCTs. The 2003 audit of CRS patients in England found that only 43.4% of sinus-only patients reported their symptoms as much better at 12-months, while 31.9% felt their symptoms to be the same or worse than before surgery. As a result 4.7% had revision surgery and a further 5.6% were on waiting lists at 12 months. (Brown et al., 2003). This compares with 2.7% and 6.9% requiring revision surgery within 12 months of surgery with XprESS and FESS respectively, as reported in a large, recently conducted RCT (Chandra et al., 2016).

To account for this difference in real world outcomes, healthcare resource utilisation in the FESS arm were sourced from the UK audit and outcomes with XprESS and Acclarent arm were estimated by applying either a relative risk or proportional adjustment using clinical trial data. At the time of this audit, FESS was the only surgical treatment available in England and as outcomes with FESS are not expected to have changed, the results of the UK audit are assumed to be representative of outcomes with FESS in a real-world English setting. Most of the clinical inputs to determine relative differences in outcomes between XprESS and FESS were sourced from the REMODEL RCT (Chandra et al., 2016),

selected as the was the largest and most robust RCT identified by the SLR conducted to accompany this economic evaluation.

Selection of clinical inputs and base-line adjustment

Similarly, specific searches were not carried out to source the cost inputs. Instead these were sourced from NHS references costs widely used in economic evaluations or internal market data collected by Entellus. All costs were vetted with UK experts and where there was uncertainty around the most appropriate sources to apply the model was programmed to select between multiple options.

3.4 Model options

The model is designed to be flexible to easily consider different scenarios and alternative assumptions. All primary model inputs (outlined in black in the model INPUTS sheet) can be changed back to the default setting by pressing the RESET button on the INPUTS sheet. In addition to being able to change any of the primary model inputs, alternatives options can easily be considered by selecting a different options where there is a drop down list, denoted by an arrow. The model options include:

- **Comparator:** The model will default to considering XprESS compared to FESS, but the user can select to compare XprESS to Acclarent
- **Anaesthesia:** The model will default to assuming all surgeries are completed in theatre under general anaesthesia but the user can select to consider a scenario where a proportion of surgeries are done under local, where all surgical costs are expected to be proportionally lower
- **Outcomes Adjustment:** The model will default to using UK audit data for the revision transition probabilities (TPs) and applying a relative risk to estimate outcomes with BCDs. Alternatively, the user can select to apply the results from REMODEL directly and assume the rates with Acclarent are the same as XprESS
- **Time Horizon**: The model will default to a 5 year time horizon but the user can select to consider any time horizon between 1 and 5, in whole year increments
- **Discount Rate Costs:** The discount rate will default to 3.5% and will be applied to all costs beyond 1 year but the user can select to change this to any value between 0% and 100%
- **Source of estimate - procedure time***:* The selected source determines the procedure time for XprESS and the comparator. The options include outcomes reported by UK expert opinion or an Italian RCT
- **Source of estimate – length of stay:** The selected source determines the length of stay after XprESS and the comparator. All options were sourced from UK HES data (HSCIC) but differ by procedure type
- **Source– % under local:** The selected source determines the percentage of surgeries conducted under local anaesthesia where the options include expert opinion or USA data

Surgical Procedure cost

Two approaches are applied to calculate the cost of a surgical procedure, excluding equipment. The base-case approach assumes all procedures are conducted in theatre under general anaesthesia, while the alternative option considers the impact if a proportion of surgeries are conducted under local anaesthesia in the ambulatory setting.

The cost of a general surgical procedure was calculated as the surgical time multiplied by the unit cost of theatre and staff time, plus the theatre consumable used during the procedure and the time spend in hospital post-surgery.

In the second approach, the cost of a surgery conducted under local was estimated by applying a ratio of the cost of day case hernia surgical procedures conducted under general and local anaesthesia respectively (Zilvetti et al., 2009) and assuming there would be a similar proportional reduction in costs between CRS surgical procedures conducted under general switched to local (excluding equipment costs). The cost of surgery was calculated as the weighted average, applying the proportion of surgeries expected to be conducted under general and local anaesthesia with each technology. For BCD devices, it was assumed that 60% of surgeries would be moved to local if XprESS was recommended in guidelines, obtained from conservative assumptions supplied by UK experts. This compares with 90% of BCD surgeries currently conducted under local in the USA. For FESS is was assumed that only 2% would be done under local as is current practice reported in the 2003 audit. This is consistent with USA data which reports that less than 5% of FESS procedures are performed under local. The inputs and sources applied are described in **Appendix 1**.

The equipment costs were calculated separately and assumed to be the same irrespective of the anaesthesia option. Unit costs and quantities for the consumables required with each intervention were sourced from Entellus market data. No capital costs for equipment were included as all other capital equipment used is expected to be standard surgical equipment applicable to all technologies and included in the unit cost of theatre time. The inputs and sources applied in the surgical health state in the base case are described in **Table 8** in **Appendix 1**.

Under both approaches the difference in surgical time was expected to be the main driver of the difference in cost. The base-case estimates were supplied by UK experts based on conducting multiple bilateral procedures in an episode of care. A scenario analysis applied the results of an Italian RCT based on only frontal sinuses. These estimate were consistent with procedure times reported in the USA from CMS database which show that for all sinus the surgical time was considerably longer with FESS compared to BCDs and is even longer when treating multiple sinuses. A more detailed description of the selection inputs is provided in **Table 13** in **Appendix 2** and the CMS procedure time data is provided in **Appendix 3**.

GP follow-up 3-months post-discharge

The TP for requiring GP follow-up with FESS was obtained from the UK audit and TPs for XprESS and Acclarent were derived by multiplying the relative risk (RR) of discharge with nasal bleed by the TP for FESS. The risk of nasal bleed was selected to derive the RR as this expected to be a good indicator of the risk of requiring healthcare resources in the short-term.

The unit cost of a GP follow up was calculated as the unit cost of a GP visit and a prescription cost, both sourced from the PSSRU 2015 (Curtis, 2015) plus a the unit cost of a prescription for a steroid nasal spray (Fluticasone propionate), a course of macrolide (Azithromycin 500 mg once daily for 3 days) and a course of macrolide (Azithromycin 500 mg once daily for 3 days)(BNF, 2016, 2016). The cost of a GP visit was multiplied by the average rate of GPs within 3 months amongst those with 1 or more visit. This rate was also obtained from the UK audit (Brown et al., 2003).

The cost of pain medication post-discharge was calculated as the days on pain medication sourced from the REMODEL RCT (Chandra et al., 2016) multiplied by the cost of pain medication per day.

A more detailed description of the GP follow-up 3 months post-discharge inputs is provided in **Table 10** in **Appendix 1.**

Readmission

Similarly, the TP for readmission after FESS was also obtained from the 2003 audit (Brown et al., 2003) which reported 4.1% of sinus patients were readmitted within three months. The same approach to adjusting the TP for FESS to calculate the TP with XprESS or Acclarent as described above for GP visits was applied, using the RR of nasal bleed.

A more detailed description of the readmission inputs is provided in **Table 11** in **Appendix 1.**

Revision and Surgical Success Health States

The TP for surgery revision after FESS was obtained from the UK audit which reported 4.1% had a revision surgery by 12 months and 15.5% had revision surgery by 5 years (Hopkins et al., 2009). The TPs for surgery revision with XprESS and Acclarent were calculated applying a RR of surgery revision with XprESS compared to FESS using the outcomes from the REMODEL (Chandra et al., 2016) RCT at one year. An alternative selection option allows the user to apply the % with revision at 12 month reported in the REMODEL study directly to derive the TPs and assume that this TP is constant over time.

The cost of the revision surgery was assumed to be the same as the initial surgical procedure cost.

Both long-term health states also included monthly costs of GP visits. The monthly rate of GP visits with FESS was obtained from the UK audit (Hopkins et al., 2006). The rate of GP visits with XprESS and Acclarent was calculated using the percentage difference in the reduction in CRS episodes events reported in the REMODEL RCT and applying this proportional difference to the rate of GP follow-ups with. All rates of GP visits beyond 3 months were assumed to be constant over time and the unit cost of a GP visit was assumed to be the same as in the first three months. A monthly rate was applied and multiplied by 9 for the period between 3 and 12 months and multiplied by 12 for all subsequent years.

A more detailed description of the revision and surgical success inputs is provided in **Table 12** in **Appendix 1**.

4 Model Results

This section reports the results of the de novo analysis comparing XprESS to FESS and Acclarent respectively.

4.1 XprESS compared to FESS

Compared to FESS, XprESS is estimated to result in savings of £1,302 per patients, mainly due to a reduction in the procedure costs. A breakdown of the cost per patient is reported in Table 1 and illustrated in **Figure 2** and **Figure 3** below. This shows that the additional cost of XprESS equipment is easily offset by cost-savings from reduced surgical procedure costs, as well as other downstream cost-savings from GP visits, readmission and revisions avoided. **Figure 4** shows cost-savings with XprESS compared to FESS over time. This shows that the majority of the cost-savings are accumulated in first year due to the difference in surgical procedure costs. There are also some further savings from reduced admissions, GP visits and revision risk.

Table 1: Base-case results XprESS compared to FESS

Comparator	Surgery excluding. Equip (£)	Equipment (£)	GP visits 3 <months (£)	Pain Mgt. (£)	Admission 3 <months (£)	GP visits beyond 3 months (£)	Revisions (£)	Total (£)
XprESS	984	900	42	0	14	511	228	2,679
FESS	2,594	300	74	0	25	590	397	3,981
Difference	1,610	-600	32	0	11	80	169	1,302

Figure 2: Total Cost, XprESS compared to FESS

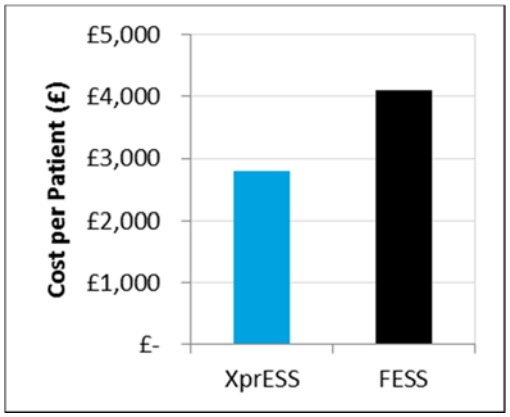


Figure 3: Breakdown of cost, by cost type XprESS compared to FESS

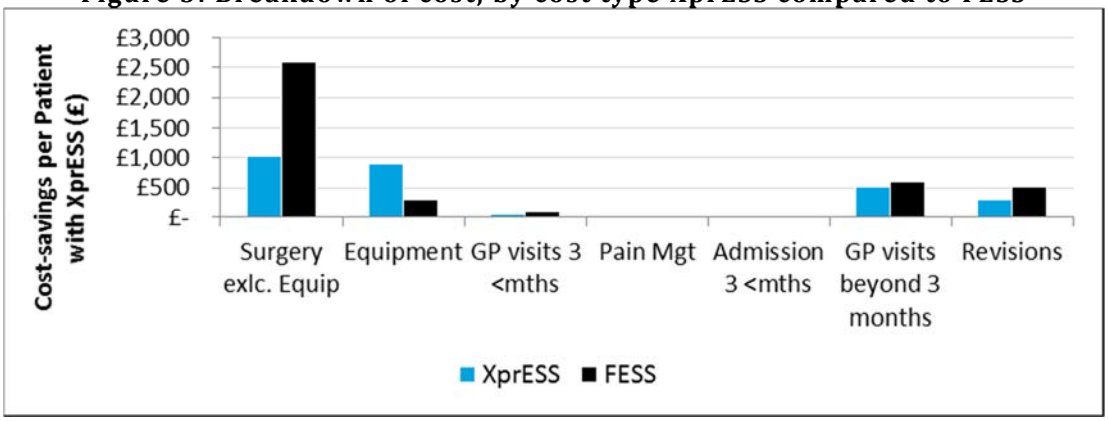
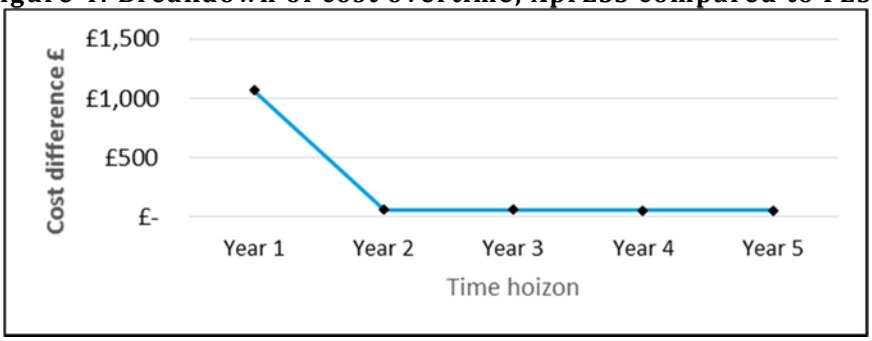


Figure 4: Breakdown of cost overtime, XprESS compared to FESS



Compared to FESS, XprESS may also result in improved outcomes. **Table 2** below reports the net difference in surgery time, % requiring GP visits or admission at 3 months and the difference in GP visits and revision and change in SNOT-score at 12 months. While the change in CRS episodes, revision rate and SNOT-score at 12-month reported in REMODEL RCT were not statistically significant they show a consistent direction of effect in favour of XprESS (Chandra et al., 2016). This suggests that XprESS results in similar or better outcomes.

Table 2: Difference in other patient outcomes, XprESS compared to FESS

Comparator	Surgery time (mins)	% require GP visits 3 <mths	% require admission 3 <mths	Rate GP visit > 3mths	% require revision at one year	Change in SNOT-score
XprESS	30.00	24%	2%	0.10	3.6%	-0.0159
FESS	90.00	42%	4%	0.12	4.1%	-0.016
Difference	60.00	18%	2%	0.02	1%	0%

4.2 XprESS compared to Acclarent

Compared to Acclarent, XprESS is also estimated to results in cost savings. **Table 3** and **Figure 5** report the total cost savings and a breakdown of total costs, by cost type. The total savings were estimated to be £531 per patients, mainly due to a reduction in the equipment cost. **Figure 6** below shows that most of the cost-savings are due to the differences in equipment costs and the surgical costs as the procedure is expected to be approximately 10 minutes shorter in the base-case where it is assumed 3 procedures are performed. While the rate of revision surgeries is expected to be the same for both procedures,

XprESS is expected to result in cost-savings compared to Acclarent due to the lower cost of revision surgery with XprESS. The costs are not reported over time here as almost all the difference in costs is accumulated in the first year, apart from a small difference in revision costs. Similarly, no other difference in outcomes is reported as all outcomes are assumed to be the same with both XprESS and Acclarent.

Table 3: Base-case results XprESS compared to Acclarent

Comparator	Surgery excluding. Equip	Equipment	GP visits 3 <months	Pain Mgt.	Admission 3 <months	GP visits beyond 3 months	Revisions	Total
XprESS	984	900	42	0	14	511	228	2,679
ACCLARENT	1,216	1141	42	0	14	511	285	3,210
Difference	232	241	0	0	0	0	57	531

Figure 5: Total cost per patient, XprESS compared to Acclarent

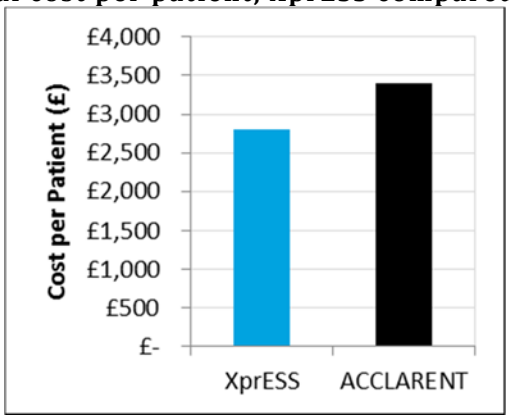
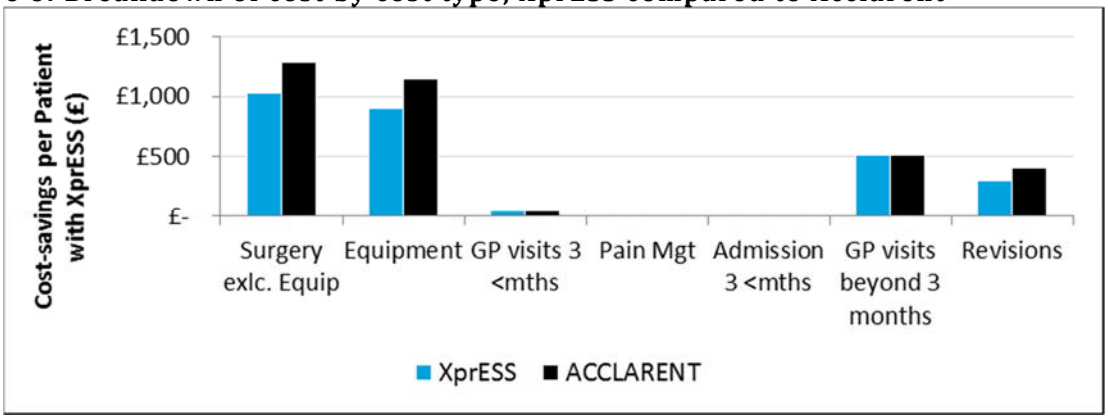


Figure 6: Breakdown of cost by cost type, XprESS compared to Acclarent



5 Deterministic Sensitivity Analysis

This section reports the results of a deterministic sensitivity analysis (DSA) conducted to quantify the uncertainty around the net difference in cost per patient in the analysis comparing XprESS to FESS and Acclarent respectively.

5.1 Method

The DSA varies each model input one at a time and re-calculates the net difference in cost per patient to evaluate the impact that varying each input has on the result. Each input is varied at a value lower and then higher than the base case input. After each input has been varied and the output ranges are compared across all variables and then ranked to present the results on a tornado plot. The variables with the greatest impact on the results are ranked first. The range of uncertainty around the net difference in cost per patient can be estimated by considering the range around the values that have the greatest impact on the result. All primary clinical inputs were included in the DSA. The upper and lower bounds were calculated by applying a 20% increase and decrease respectively.

5.2 Deterministic Sensitivity Analysis (DSA) results

XprESS compared to FESS

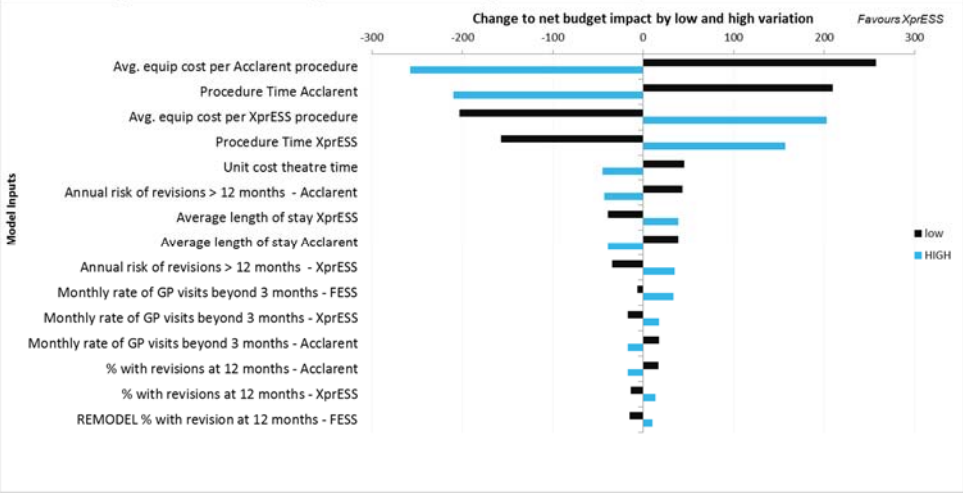
The results of the DSA comparing XprESS to FESS are illustrated in **Figure 7** and the range of costs savings with XprESS found by the DSA are reported in **Table 4** below.

These results show that varying the inputs for procedure time with FESS and the unit cost of theatre time have the largest and second largest impact on the net budget impact per patient result, respectively. Varying the input for procedure time with FESS by 20% varies the net budget impact per patient between £1,044 and £1,559. Varying any other input by 20% does not exceed this range. This validates the conclusion that XprESS is very likely to result in cost-savings of at least £1,000 per patients and may be much higher.

Table 4: Range of cost-savings reported in the DSA for XprESS compared to FESS

	Base-case £	Lowest estimate £	Highest Estimate £
Range of cost-savings with XprESS compared to FESS	1,302	1,044	1,559

Figure 7: Tornado plot of DSA reported for XprESS compared to FESS



XprESS compared to Acclarent

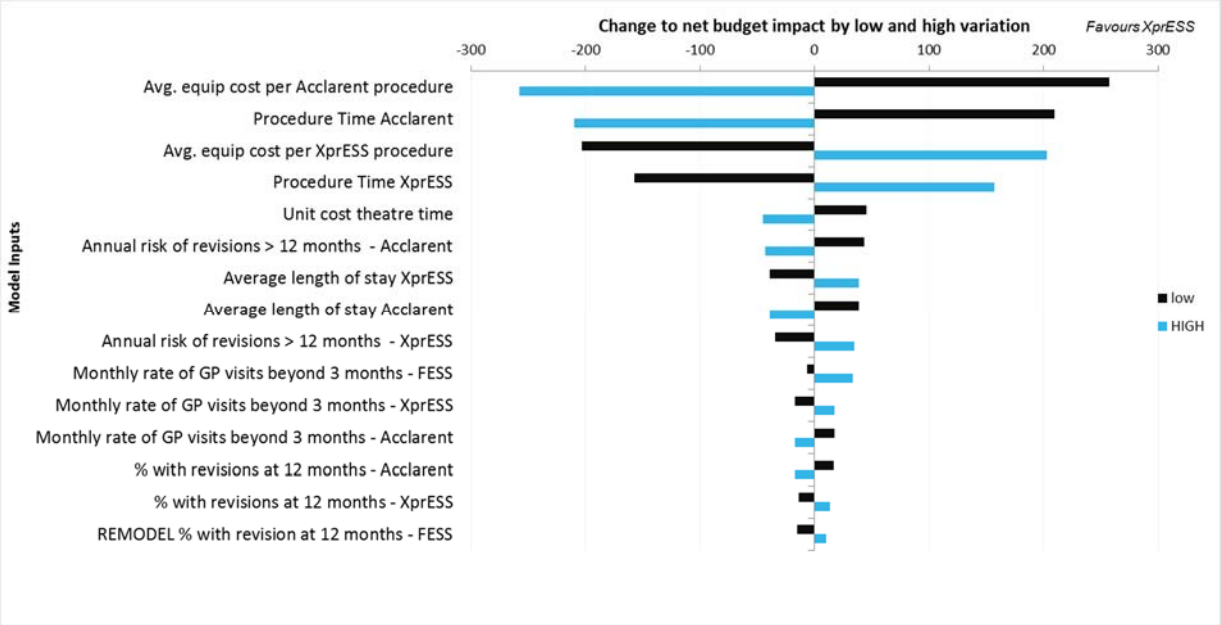
The results of the DSA comparing XprESS to Acclarent are illustrated in **Figure 8** and the range of costs savings with XprESS found by the DSA are reported in **Table 5** below.

Unsurprisingly, varying the equipment cost for Acclarent and the procedure time with Acclarent have the greatest impact on the potential cost savings, as most other inputs are assumed to be equal for XprESS and Acclarent. Varying the equipment cost for Acclarent by 20% varies the net budget impact per patient between £274 and £784. No input varied by 20% resulted in a negative budget impact this therefore supports the conclusion that XprESS is very likely to be cost-savings compared to Acclarent.

Table 5: Range of cost-savings reported in the DSA for XprESS compared to Acclarent

	Base-case £	Lowest estimate £	Highest Estimate £
Range of cost-savings with XprESS compared to Acclarent	531	274	784

Figure 8: Tornado plot of DSA reported for XprESS compared to Acclarent



6 Scenario Analysis

This section reports the results when all selection options in the model are applied, keeping all other base-case assumptions are kept constant.

6.1 Cost savings under different time horizons

Table 6 reports the cumulative cost-savings with XprESS compared to both technologies over different model time horizons. In both cases, the cost-savings increase with longer time horizons, due to lower costs for GP visits and revisions with XprESS compared to FESS and Acclarent. Neither comparisons are particularly sensitive to the time horizon as in both scenarios most of the costs occur in year 1.

Table 6: Cost savings under different time horizons

Time Horizon	XprESS vs. FESS (£)	XprESS vs. Acclarent (£)
1 year	1,117	491
2 year	1,167	502
3 year	1,215	512
4 year	1,259	522
5 year (Base)	1,302	531

6.2 Cost savings under different option selections

Table 7 reports the cost-savings per patients with XprESS compared to both technologies when alternative options from the base-case default settings are selected. The following observations can be made from these results:

- When the option to include anaesthesia is selected the cost-savings are even greater with XprESS compared to FESS. This is because if conducting surgeries under local was a recommended pathway, most BCD surgeries are expected to be done under local, while most FESS procedures would still need to be conducted under general in theatre. Changing this option has minimal impact of the results for XprESS compared to Acclarent
- Applying the REMODEL results directly, slightly decreases the cost-savings with XprESS compared to both comparators. This is because accounting for the higher UK base-line rates inflates any cost savings with XprESS, as XprESS is associated with lower revision rates and less costly revision surgeries
- Applying the results of the Italian RCT reduces costs savings with XprESS for both technologies but still supports the conclusions that XprESS is cost-saving. This scenario is expected to reflect the lowest difference in procedure time compared to both technologies as this study only captures the difference in surgery time when treating a frontal sinus. In reality the difference in procedure time is expected to be much higher when multiple sinuses are treating in one episode, as is common practice in the NHS.
- Varying the source of the time to discharge inputs changes the estimated cost-savings with XprESS compared to FESS but did not impact the conclusion that XprESS was cost-saving. This is because the difference in time to discharge was relatively consistent under all procedure codes. In all procedure codes the time to discharge was shorter with a BCD plus FESS compared to FESS.
- Changing the source of the % of procedures conducted under local anaesthesia and applying the rates reported in the USA increases the potential cost-savings with XprESS compared to FESS. This is because a conservative assumption was applied in the base-case as this practice is not

common in the UK. This suggests that the cost-savings may be even higher if there is a shift to conduct most XprESS surgeries under local, similar to trends in the USA.

- Changing the unit cost of theatre time to a low estimate decreases the potential cost-savings associated with XprESS considerably, however even applying this very low estimate XprESS results in cost-savings compared to FESS. The low estimate applied was obtained from a Hernia costing study where the theatre costs are expected to be lower than for CRS surgery. In reality, the cost of theatre time is expected to vary widely by hospital and by procedure type and is likely to be close to the base-case for most hospitals.

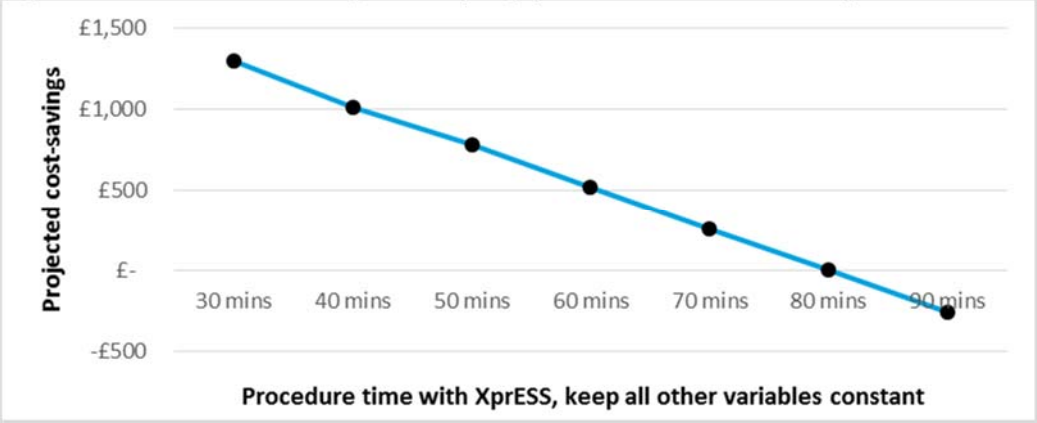
Table 7: Costs savings under different option selections

Option	Default	Results under alternative option		
		Option	XprESS vs. FESS (£)	XprESS vs. Acclarent (£)
Base	All defaults	NA	1,302	531
Anaesthesia	General only	Include local	1,520	470
Outcomes Adjustment	UK Adjustment	REMODEL unadjusted.	1,222	504
Source of estimate - procedure time	UK Experts	Italian RCT	550	257
Source of estimate - length of hospital stay	E148 frontal sinus	E133 Intra. Antro.	1,205	531
Source of estimate - % under local	UK expert opinion	USA data	1,302	531
Unit cost theatre time (per min)	Average surgery	Low cost surgery	367	352

6.3 Breakeven analysis – surgical time

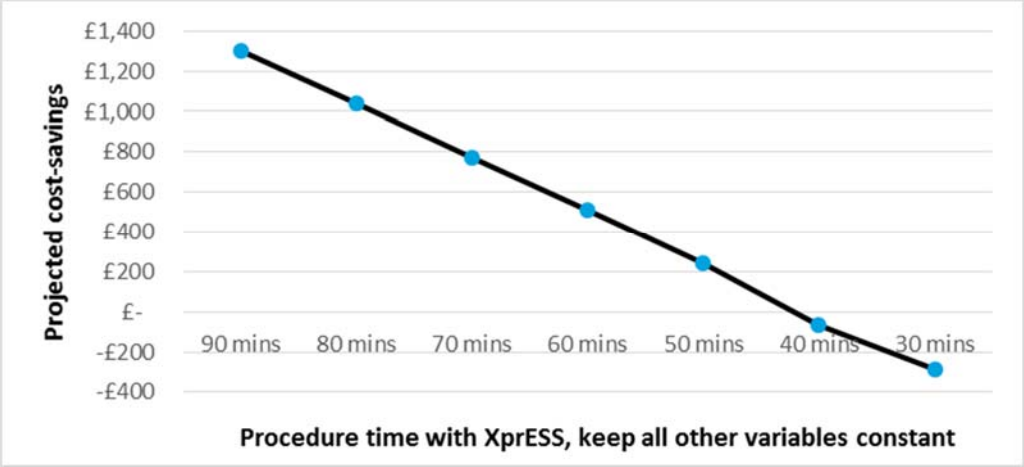
Figure 9 below illustrates the results of a breakeven analysis whereby the input for the procedure time with XprESS was varied while keeping all other inputs constant. Applying the goal seek function in excel found that XprESS was cost-neutral with a procedure time of 80 minutes and was more expensive at procedure times above this. As all estimates reported by UK experts, the Italian study and CMS databases consistently reported the procedure time with XprESS as lower than 80 minutes, this break-even analysis validates the conclusions that XprESS is expected to be cost-savings compared to FESS.

Figure 9: Breakeven analysis varying procedure time with XprESS



As there could be a possible difference around the specific procedure time with FESS, this input was also varied to demonstration a breakeven analysis and the results are presented in Figure 10 below. This displays that XprESS is cost neutral or cost-savings for any procedure time with FESS above 41 minutes. This is much lower than the estimates provided by our clinical experts of 90 +/- 15 minutes. This therefore also validates the conclusion that XprESS is likely to result in cost-savings.

Figure 10: Breakeven analysis varying procedure time with FESS



7 Discussion & Limitations

This section summarises and discusses the implications of these results and acknowledges the possible limitations of this analysis.

7.1 Comparison against FESS

The results of this de novo analysis show that XprESS results in cost-savings of approximately £1,300 per patient compared to FESS, for average risk where multiple sinuses are treated in one episode of care. Most of these cost-savings are due to reduced time in theatre and faster recovery but also include cost-savings from reduced healthcare utilisation and fewer surgical revisions.

This estimate of cost-savings is expected to be conservative as this does not include the impact of conducting a high proportion of XprESS surgeries under local anaesthesia. The potential cost-saving may be as high as £1,500 if more than half of XprESS surgery are conducted under local anaesthesia in an ambulatory setting, as is expected if this becomes a recommended pathway. As most hospitals already have and underutilize ambulatory surgical rooms, moving surgeries to an ambulatory setting is not expected to require significant service redesign and should result in considerably greater cost reductions.

Conducting more surgeries with XprESS is also expected to improve future resource utilisation by reducing future GP visit and revision costs. While there was not a statistically significant difference in CRS episodes and revisions rates found in the REMODEL RCT, there was a direction effect favour of XprESS in respect to these outcomes. This is particularly relevant to decision maker in England, where the revision rates and post-surgery CRS episodes with FESS are higher than rates reported in clinical trials. The impact of this was considered in this analysis and suggests that in addition to lower procedure cost, XprESS may also result in downstream cost-savings.

The rates and costs of the revisions rates with FESS applied in the model are expected to be conservative assumptions therefore in practice the cost-savings may be even higher. The rates applied were obtained from the 2003 Audit which reported 5-year revision rates of 15.5%, but more recent studies suggest that revision rates with FESS in the UK may be as high as 20.1% (Philpott et al., 2015). If this was the case, the cost-savings with XprESS would be even higher compared to FESS.

In addition to the cost-savings per patient, reducing the time in theatre and days in hospital may also reduce hospitals waiting lists and avoid hospital fines. As surgery with XprESS is faster and patients are discharged faster, this strategy would allow hospital to perform more procedures and potentially reduce their waiting time.

The opportunity to improve the efficiency of the surgical pathway may also has important implications for patient outcomes. As detailed in section 1.3 above there is a growing body of evidence suggesting that earlier surgical intervention is associated with improved patient outcomes and reduced healthcare use (Benninger et al., 2015, Hopkins et al., 2015). If waiting lists are the main reason for delayed access, reducing surgical and recovery times may allow more patients to be treated reducing the time spend on waiting lists.

This conclusion that XprESS is cost-saving relative to FESS is expected to be robust as this has been validated through extensive sensitivity analysis. This included one-way analysis of all model inputs, scenario analysis to consider the impact of applying alternative sources and break-even analysis for the

procedure time inputs. In all one-way sensitivity and scenario analyses, XprESS was consistently found to be cost-saving compared to FESS. Furthermore, break-even analysis validated that XprESS is cost saving at all plausible procedure times for XprESS and FESS.

7.2 Comparison against Acclarent

This de novo economic analysis also found that XprESS is likely to be cost-saving compared to Acclarent. As there is no head-to-head comparisons of XprESS compared to Acclarent, this analysis was limited to considering differences in equipment costs and the length of time in theatre when conducting multiple procedures. This analysis found that XprESS is expected to result in cost-savings of over £500 per patient.

Sensitivity analysis showed that costing savings may vary between £300 and £800 but supported the conclusion that XprESS results in cost-savings when each input was varied by 20% in either direction.

This conclusion has less implications to UK decision makers as the Acclarent BCD is no longer distributed in the UK.

7.3 Model Strengths

The strength of this de novo economic analysis include the model structure, the applicability to UK decision makers and the robustness of the scenario analysis, as detailed below:

- The model structure has been designed to capture all relevant costs and outcomes. In addition to the costs incurred in hospital the model also considered all short and medium-term resource utilisation. This enables decision-makers to consider the full impact of switching from FESS to XprESS on all healthcare utilisation.
- All inputs and assumptions have been selected to reflect resource utilisation from an NHS payer perspective. The resource utilisation in the standard care (FESS) arm were mainly obtained from follow-up of the 2003 UK audit of CRS surgeries and the outcomes for XprESS were estimated by applying relative differences obtained from a large RCT. As such, the results are expected to reflect cost-savings if XprESS was rolled out widely in England.
- An additional advantage of the model structure is the flexibility to consider alternative sources for all key model assumptions. This has facilitated extensive scenario analysis to validate the model results.

7.4 Model Limitations

The conclusions of this analysis are expected to be robust as they have been tested against sensitivity analysis and multiple scenarios were considered. Nonetheless, there are possible limitations that should be considered which are listed below:

- There is limited published research on the procedure times for conducting multiple procedures with each intervention. The base-case results were obtained from estimates provided by UK clinicians and are expected to reflect real-world outcomes. Given the uncertainty around these inputs, these were tested in a break-even analyses which showed that all plausible estimates supported the conclusion that XprESS is cost-saving compared to FESS.
- There may be uncertainty regarding the relative difference in outcomes between XprESS and FESS beyond two years as this was the duration of the main RCT applied in the model. The model assumes that the relative difference between XprESS and FESS is constant beyond 12 months. This assumption is well justified on the grounds that clinical studies show symptom improvement remains stable from as early as 1 week post standalone balloon procedure out to

2 years. Similarly, improvement in HRQoL scores after FESS do not appear to change between 6 months and 20 months [9]. As such, it is reasonable to assume that any difference in XprESS compared to FESS at 12 months is expected to be constant over time.

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Appendix 1. Model Inputs

Table 8: Default Inputs for Surgical Health State, under general

Input	Value	Reference
Procedure Time XprESS: The time in surgery with XprESS, reported in minutes	30 mins*	**Expert Opinion:** Option input that defaults to an assumption provided by UK experts, as this is expected to reflect current practice in the UK.
Procedure Time FESS: The time in surgery with FESS, reported in minutes	90 mins*	**Expert Opinion:** As above
Procedure Time Acclarent: The time in surgery with Acclarent, reported in minutes	40 mins*	**Expert Opinion:** As above
Average length of stay XprESS: The time in surgery with Acclarent, reported in minutes	0.43 days*	**HES data (HSCIC)**: Option input that defaults to applying the length of stay with a E148 frontal sinus procedure.
Average length of stay with FESS	0.97 days*	**HES data (HSCIC):** As above
Average length of stay with Acclarent	0.43 days*	**HES data (HSCIC):** As above
Unit cost theatre time per min	£20*	**NHS Institute for Innovation and Improvement(III, 2009):** Option input that defaults to the average hourly operating cost of £1200 per theatre reported by the Institute for Innovation and Improvement
Unit cost surgeon's time per min	£1.76	**PSSRU 2015(Curtis, 2015):** Surgical time per minute excluding qualification costs
Unit cost nurses time per min	£1.46	**PSSRU 2015(Curtis, 2015):** cost per minute of patient contact time with Band 5 nurse, excluding qualification costs
Unit cost of drapes & gowns per surgery: Unit cost of drapes and gowns used during 1 surgical procedure	£80	**Estimate**. Estimate based on list prices reported by Medisave.co.uk; Assuming drapes and gowns @ £40 for 1 surgeon and 1 nurse
Unit cost of tray /camera per surgery	£35	**NHS Institute for Innovation and Improvement(III, 2009):** report estimated cost of surgical trays cost £35 per surgery
Unit cost of tray /camera per surgery	£400	**Deltex Medical(2006):** report estimated the average cost of an NHS surgical bed was £400
Avg. equip cost per XprESS procedure: The average cost of all consumable equipment used in a XprESS surgical procedure	£900	**Entellus Market data:** Includes the cost of one XprESS Balloon; costs sourced from ENTELLUS internal market data
Avg. equip cost per FESS procedure: The average cost of all consumable equipment used in a FESS surgical procedure	£300	**Entellus Market data:** Includes the cost of 1 FESS Micro-blades and 1 blur; costs sourced from ENTELLUS internal market data
Avg. equip cost per Acclarent procedure: The average cost of all consumable equipment used in an Acclarent surgical procedure	£1141	**Entellus Market data:** Includes the cost of one Acclarent Balloon, 1 guide catheter, 1 lavage device and 1 inflation device; costs sourced from ENTELLUS internal market data

*indicates that an alternative option may be selected. All option inputs are detailed in Appendix 2

Table 9: Default Inputs for Surgical Health States, with local

Items	Value	Reference
% under local XprESS Refers to the proportion of surgeries expected to conducted under local and is only applicable if the input "Consider local anaesthesia" is toggled to "include local"	60%	Expert opinion.
% under local FESS As above, refers to the proportion of surgeries expected to conducted under local with FESS	0%	Expert opinion
% under local Acclarent As above, refers to the proportion of surgeries expected to conducted under local with FESS Acclarent	60%	Expert opinion
Cost ratio between local and general anaesthesia procedures. Assumption for the cost ratio between surgical procedures conducted under local compared to general anaesthesia	0.631	**Zilvetti et al. 2009**(Zilvetti et al., 2009) Calculated as the ratio between the costs of a day case hernia procedures conducted under local (£640) and general (£1015) anaesthesia respectively
Unit cost of procedure under general - XprESS	£984	**Model Calculation**. Calculated as the time in surgery under general multiplied by the unit cost of theatre time, a surgeon's time and a nurse's time plus the cost of drapes, gowns and trays plus the average days in hospital after surgery with XprESS multiplied by the unit cost of a hospital day
Unit cost of procedure under general - Fess	£2594.00	**Model Calculation.** As above, applying the time in surgery with FESS and the average time in hospital after surgery with FESS
Unit cost of procedure under general - Acclarent	£1404.33	**Model Calculation.** As above, applying the time in surgery with Acclarent and the average time in hospital after surgery with Acclarent

Table 10: Default Inputs for GP Follow-Up Health State

Items	Value	Reference
RR nasal bleed. This input is used to adjust the proportion of patients requiring a GP visit or hospital admission with FESS to calculate these inputs for FESS	0.57	**REMODEL RCT(Chandra et al., 2016)**. Derived from the results of the REMODEL RCT by dividing the risk of nasal bleed with XprESS by the risk of nasal bleed with FESS.
% needing GP visits within 90 days - XprESS	24%	**REMODEL RCT(Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Calculated as the probability of a GP visits 3 months post-surgery with FESS, adjusted using the RR nasal bleed input
% needing GP visits within 90 days - FESS	42%	**UK Audit (Brown et al., 2003).** The probability of requiring a GP visit was sourced from Brown et al. 2003, based on the findings of a UK audit of CRS surgeries,

		where all surgeries were assumed be completed with FESS
% needing GP visits within 90 days - Accelerant	24%	Assumed to be the same as XprESS
Rate of GP visits in first 3 months	1.861	**UK Audit (Brown et al., 2003)** Calculated based on the proportion reported to attend the GP,1 to 3 or more times within 3 months of CRS surgery
Unit cost of GP visit	£94.43	**PSSRU 2015, BNF, Expert opinion.** Calculated as the unit cost of a GP visit and a prescription cost, both sourced from the PSSRU 2015 (Curtis, 2015) plus a the unit cost of a prescription for a steroid nasal spray (Fluticasone propionate), a course of macrolide (Azithromycin 500 mg once daily for 3 days) and a course of macrolide (Azithromycin 500 mg once daily for 3 days). Prescription assumptions were supplied by UK experts and prescription costs were sourced from the British National Formulary (BNF), 2016 (BNF, 2016, 2016)
Days on pain medication - XprESS	1	REMODEL RCT **(Chandra et al., 2016)**
Days on pain medication - FESS	2.8	REMODEL RCT **(Chandra et al., 2016)**
Days on pain medication - Accelerant	1	Assumption. Assumed to be the same as XprESS
Unit cost of pain medication	£0.13	**BNF, Expert opinion.** Assumed to be treated with 400mg Ibuprofen three times a day, an assumption provided by UK experts. Unit costs were obtained from the BNF, 2016

Table 11: Default Inputs for Readmission Health State

Items	Value	Reference
% readmitted – XprESS: The probability of a readmission for a nasal procedure within 3 months of CRS surgery with XprESS	2.3%	**REMODEL RCT(Chandra et al., 2016) & UK Audit (Brown et al., 2003).** Calculated as the probability of a readmission post-surgery with FESS, adjusted using the RR of nasal bleed
Transition probability readmitted - FESS	4.1%	**UK Audit (Brown et al., 2003).** The probability of readmission within 3 month of surgery was sourced from Brown et al. 2003, based on the findings of a UK audit of CRS surgeries, where all surgeries were assumed be completed with FESS
Transition probability readmitted - Accelerant	2.3%	Assumed to be the same as XprESS
Unit Cost per readmission	£601	**NHS Reference cost 2011-12.(Gov.uk, 2011-12)** Reference costs CZ12V – Minor Nose Procedures, 19 years and over with CC, reference price for non-elective admission. This year was selected for estimating the costs as prior to 2012-13 references prices were calculated as an average across hospitals.

Table 12: Default Inputs for Revision and surgery success Health State

Items	Value	Reference
Percentage difference in rate of CRS event. Percentage difference in the rate of CRS event post-surgery with XprESS compared FESS. This input is used to adjust the proportion of patients requiring a GP visit between beyond 3 months	-13.5%	**REMODEL RCT (Chandra et al., 2016)** Derived from the results of the REMODEL RCT as the difference between the changes in CRS events with XprESS compared to FESS, divided by the change in CRS events with FESS.
Monthly rate of GP visits beyond 3 months with XprESS	0.10	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Calculated as the monthly rate of GP visit with FESS beyond 3 months, adjusted using the percentage difference in the rate of CRS events. This rate is assumed to be constant over time
Monthly rate of GP visits beyond 3 months - FESS	0.12	**UK Audit (Brown et al., 2003)** Calculated using the proportion reported to attend the GP one to three or more times beyond three months of CRS surgery in the2003 UK audit (Brown et al. 2003). Annual rates were converted to monthly rates. This rate is assumed to be constant over time
Monthly rate of GP visits beyond 3 months - Acclarent	0.10	**Assumption.** Assumed to be the same as XprESS
REMODEL % with revision at 12 months - XprESS	1.4%	**REMODEL RCT (Chandra et al., 2016)** Obtained from the REMODEL RCT using the percentage with revision at 12 months following surgery with XprESS. This annual probability was assumed to be constant over time
REMODEL % with revision at 12 months - FESS	1.2%	**REMODEL RCT (Chandra et al., 2016)** As above, using the same measure reported for FESS.
REMODEL % with revision at 12 months - Acclarent	1.4%	**Assumption.** Assume to be the same as with XprESS
Relative risk of revision	.875	**REMODEL RCT (Chandra et al., 2016)** Calculated as the risk of revision with XprESS divided by the risk of revision with FESS, where both inputs are sourced from the REMODEL RCT
% with revisions at 12 months - XprESS	3.6%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Calculated as the annual probability with FESS multiplied by the relative risk of revision with XprESS
% with revisions at 12 months - FESS	4.1%	**UK Audit (Brown et al., 2003)** The base-case defaults to estimating outcomes in a UK setting. This rate for FESS was obtained from 1 year follow up of the UK audit (Brown et al. 2003)
% with revisions at 12 months - Acclarent	3.6%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Assumed to be the same as XprESS
Annual risk of revisions > 12 months - XprESS	3.3%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)**Calculated as the annual probability with FESS multiplied by the relative risk of revision with XprESS
Annual risk of revisions > 12 months - FESS	3.8%	**UK Audit (Brown et al., 2003)** This rate for FESS was obtained from 5 year follow up of the UK audit (Brown et al. 2003). The proportion that had a revision by one year was subtracted by the proportion that had a

		revision by 5 years and divided by 4 to derive an annual probability beyond 1 year
Annual risk of revisions > 12 months - Acclarent	3.3%	**REMODEL RCT (Chandra et al., 2016) & UK Audit (Brown et al., 2003)** Assumed to be the same as FESS

Appendix 2: Selection Option Descriptions

Table 13: Surgical time options

Procedure time				
Option	**XprESS**	**FESS**	**Acclarent**	**Source / Assumption**
UK expert opinion	30 min	90 min	40 min	The base-case considers the procedure time for treating multiple sinuses and defaults to applying UK expert opinion. In the UK, when treating CRS patients multiple procedures are typically performed in one episode of care setting. As reported by the UK HES database, in some cases up to 7 individual procedures are performed within one episode of care and on an average, 2.75 procedures are performed per episode [HSCIC HES]. With FESS each procedure requires additional work, extending the time in theatre. Similarly with Acclarent, additional catheters are required when treating more than one sinus, which extends theatre time. In contrast, with the XprESS device multiple sinuses can be treated with the same catheter, hence minimal additional theatre time is required to advance and treat additional sinuses in the same episode of care. The estimated operative time based on feedback from UK physicians for an average episode of care with XprESS is 30 +/-5 minutes, with FESS is 90 +/- 15 minutes and with Acclarent is 40 +/-5 minutes. This estimate for FESS is consistent with procedures time of 42 minutes with FESS for unilateral reported in UK audits (Hopkins 2006), assuming that an average episode of care requires a bilateral approach and multiple sinuses treated (thus requiring considerably more time to perform both sides).
Italian RCT	32 min (same as Acclarent)	65 min	32 min	A scenario analysis consider the procedure time for treating only the fontal sinus, using the procedure times reported in a recent Italian RCT (Marzetti et al., 2014). This study captured procedure times with FESS and a BCD when treating a frontal sinus. Due to the work involved in treating the frontal sinuses, the time normally allotted to treat tends to be the longest. Here the procedure time with FESS was

				found to be 65 +/- 15 minute and with a BCD 32 +/- 15 min. The procedure times for treating a single sinus are assumed to be the same for both BCD technologies as no additional catheters are required. There is only expected to be a difference in procedure time between BCD technologies when more than one sinus is treated. However, even when treating a single sinus the procedure time is almost doubled with FESS compared to XprESS. This defences in procedure time is even greater when multiple sinuses are treated in one episode of care, as is the norm in the UK.

Table 14: Length of hospital stay options

Average length of hospital stay				
Option	**XprESS**	**FESS**	**Acclarent**	**Source / Assumption**
E148 Frontal sinus	0.43	0.97	0.43	Recovery times with FESS and BCDs were obtained from three difference episodes of care codes. The code for E148 frontal sinus was applied in the base-case as the highest volume of BCD procedures were reported under this code. The other was considered in scenario analyses
E133 Intra. Antro.	0.27	0.60	0.27	

Table 15: % of surgeries conducted under local options

% conducted under local			
XprESS	**FESS**	**Acclarent**	**Source / Assumption**
60%	2.1%	60%	The UK audit data reported that only 2.1% of FESS are done under local. Expert opinion anticipates that +60% of BCD procedures would move to local if XprESS was the recommended CRS surgical procedure
91.3%	1%	91.3%	Obtained from Medicare data on the proportion of sinus procedures conducted in an office setting with each technology

Appendix 3: USA Data on Procedure Times for FESS and Standalone Balloon Dilation

Data obtained from the Center for Medicare & Medicaid Services (CMS) federal agency that runs the Medicare Program. CPT Codes for CRS surgery and the average procedure time for each code are detailed below. Codes for Standalone Balloon Dilation became effective 1-1-2011.

Table 16: Description of CPT codes

CPT codes	Short Description of Code
FESS	
31256	Exploration maxillary sinus
31267	Endoscopy maxillary sinus
31276	Sinus endoscopy surgical
31287	Nasal/sinus endoscopy surg
31288	Nasal/sinus endoscopy surg
Standalone Balloon Dilation	
31295	Sinus endo w/balloon dil
31296	Sinus endo w/balloon dil
31297	Sinus endo w/balloon dil

Table 17: Procedure time by CPT code

CPT codes are based on each specific sinus unilateral, the time is per sinus treated to determine work component in the physician fee schedule. Times were calculated based on AMA RUC /society survey process.

Cpt code	Pre. Eval. Time	Pre. Posit. time	Pre-Service Scrub Dress Wait time	Median Intra Service time	Immediate _post Service time	Total_ time	Comments
	mins	*mins*	*mins*	*mins*	*mins*	*mins*	
31295	30	3	10	**20**	15	78	
31296	30	3	10	**30**	15	88	
31297	30	3	10	**28**	15	86	
31256	18	0	15	**45**	18	96	
31267	30	0	0	**50**	30	110	Maxillary FESS most commonly reported
31276	30	0	0	**75**	30	135	
31287	30	0	0	**45**	30	105	
31288	30	0	0	**60**	30	120	Sphenoid FESS most commonly reported

Treatment is usually performed bilateral (both sides LT and RT) and multiple sinuses treated in a typical session. References from the 2016 Federal Ruling:

- 80 Fed. Reg. 70885 (October 30, 2015), CMS-1631-FC: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/PFS-Federal-Regulation-Notices-Items/CMS-1631-FC.html
- CY 2016 Physician Fee Schedule Work Time: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/Downloads/CY2016-PFS-FC-Work-Time.zip

Appendix 4: USA data on Site of Service Mix for FESS and Standalone Balloon Dilation

Medicare Fee-for-Service Physician Data

Table 18: Claims data from CT 2014 (latest data available)

Number of procedures **FESS** (CPT codes: 31256,31267,31276,31287,31288)	%	Site of Service
77,353	**95%**	Ambulatory outpatient setting
3,207	**4%**	In-patient- overnight
960	**1%**	Office
Standalone Balloon Dilation (CPT codes:31295,31296,31297)	**%**	**Site of Service**
4,925	**8.5%**	Ambulatory outpatient setting
89	**0.2%**	In-patient- overnight
52,836	**91.3%**	Office

Of note, data is based on CY 2014 and the standalone codes were new in 2011, USA ENT's surgeons are still transitioning appropriate FESS procedures to standalone balloon procedures and total volume of BCD's vs. FESS procedures mix would be higher today.

Reference:
Direct Research, LLC analysis of Medicare 2014 allowed services by site (Summarized from Physician/supplier procedure summary master file).

Device Access

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UK Overview
FESS and Balloon Dilation For Entellus Medical

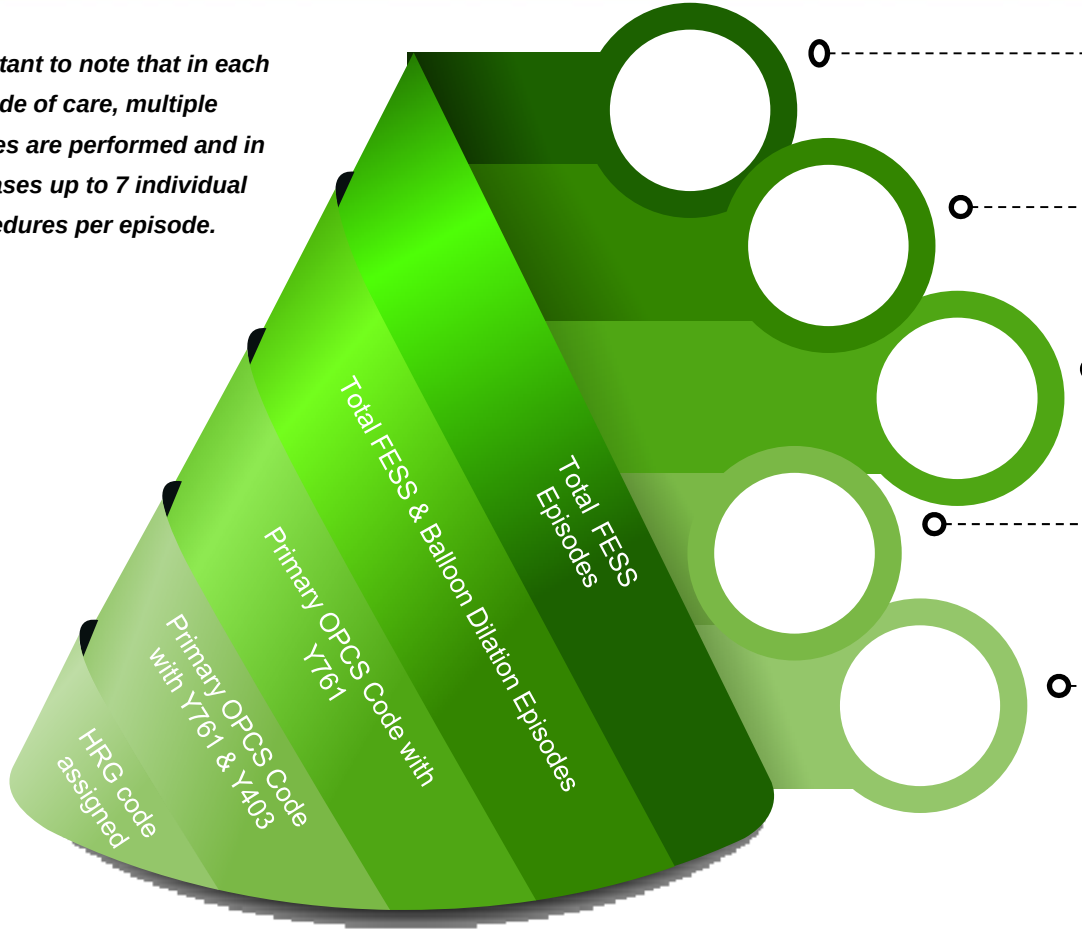
By

Richard Tuson & Michael Branagan-Harris

16th June 2015

Overview of FESS & Balloon Dilation

It is important to note that in each episode of care, multiple procedures are performed and in some cases up to 7 individual procedures per episode.



Apr 13 to Mar 14 = 16,299 Episodes
Apr 14 to Jan 15 = 13,010 Episodes

Apr 13 to Mar 14 = 327 Episodes
April 14 to Jan 15 = 259 Episodes

Main Primary OPCS Code with secondary code of Y761
Example – E14.2 Intranasal Ethmoidectomy

Main Primary OPCS Code with secondary code of Y761 & Y403
J32.9 Chronic sinusitis unspecified

HRG Code = CZ14Y or CZ14V

Episode definition = Please note that an Episode of care is a theatre event and not unique patients or procedure. Therefore this number can not be used to calculate total patients. However it will be the total number of events which have been reimbursed

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Coding Required

Summary

The coding for both surgical events need to have a Y76.1 code to identify the FESS approach. However when a Balloon is used to support a Sinus operation, then the coders must include a Y40.3 code.

However this is a standard balloon dilation code, as there is not a separate code for a sinus procedure

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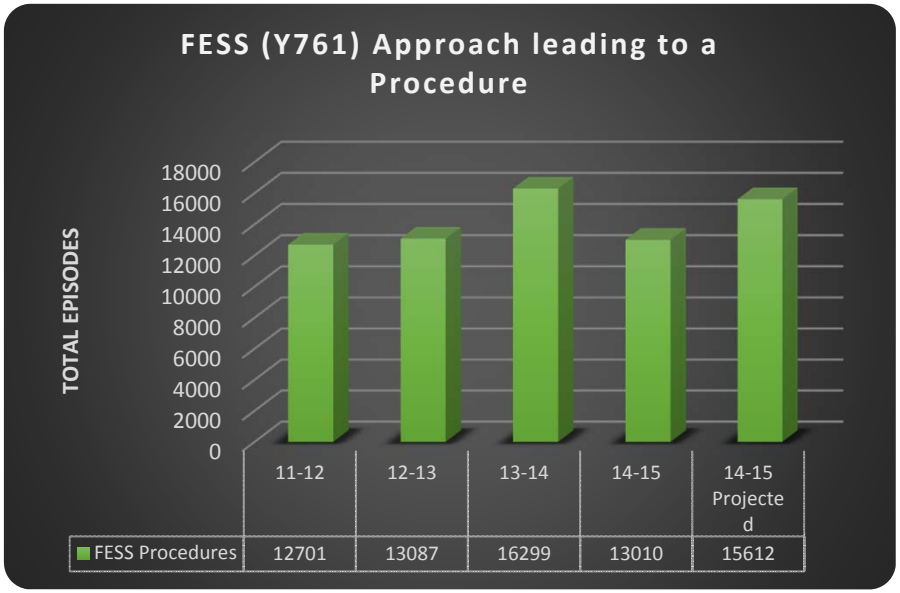
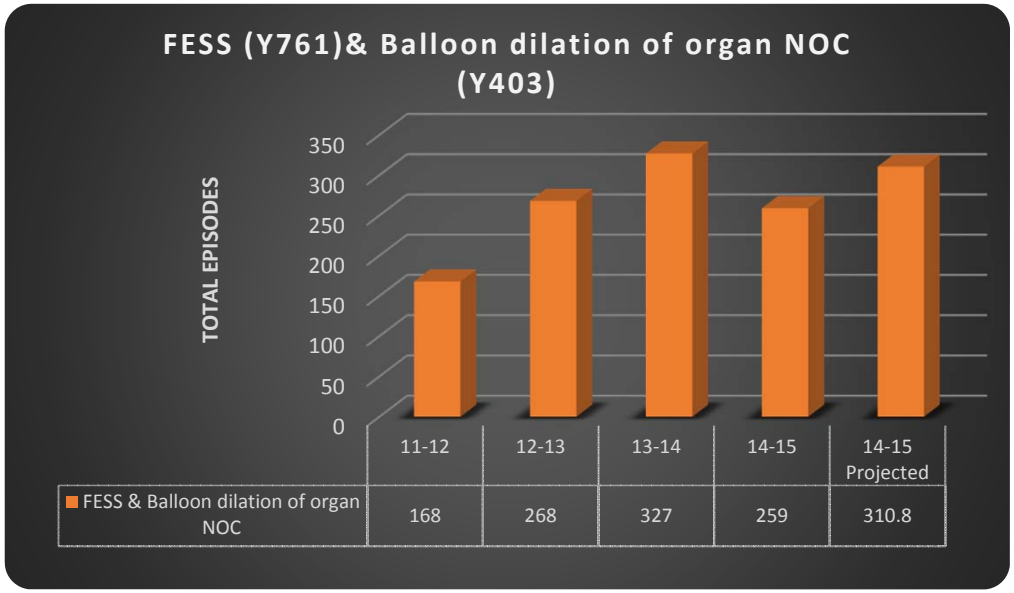
Activity Levels FESS & Balloon Dilation





All activity numbers are sourced from HSCIC HES data. 14-15 are projected based on Apr 14 to Jan 15 extrapolated to a full 12 months.

Device Access
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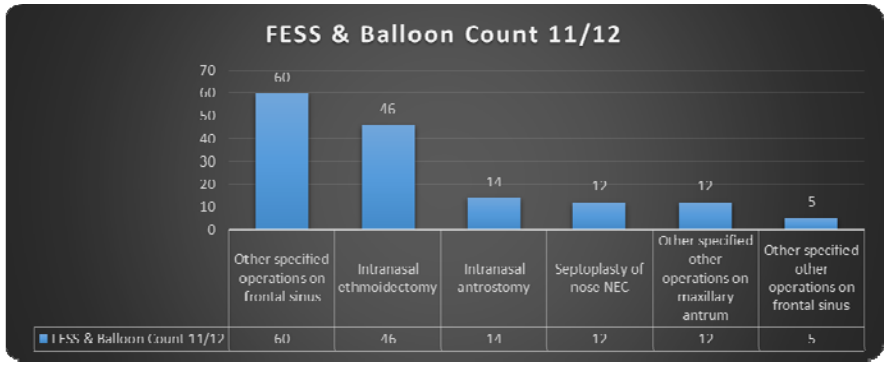
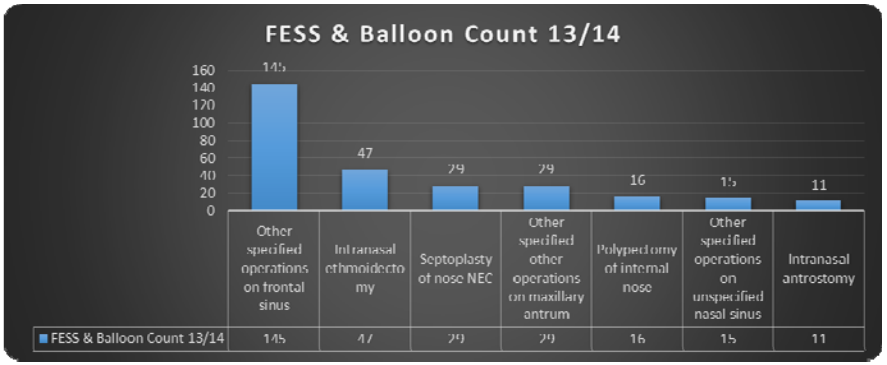
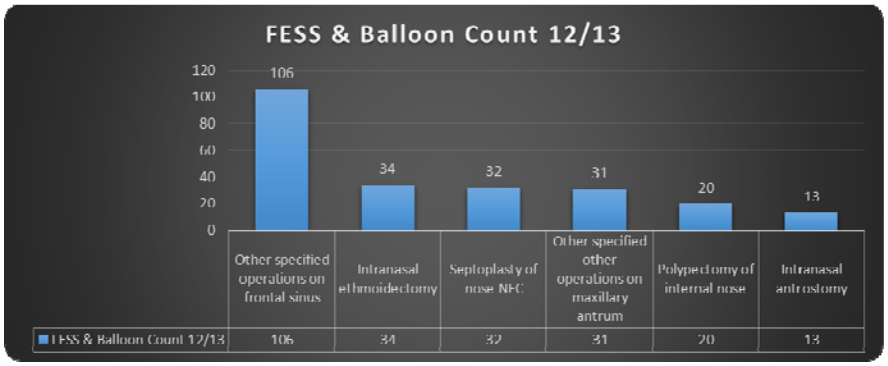
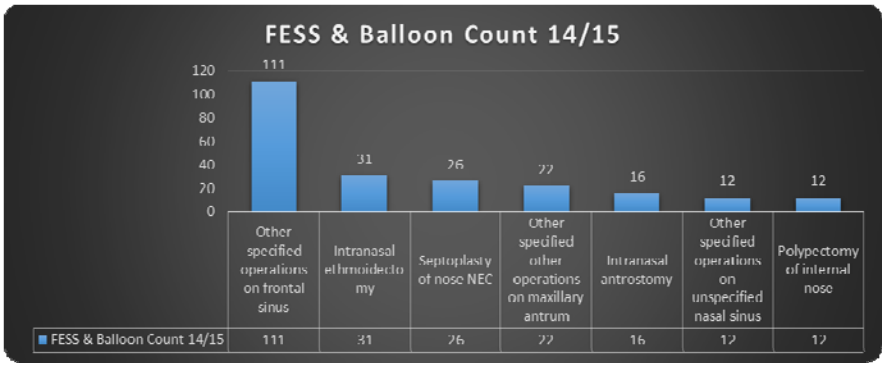
Activity Levels FESS & Balloon Dilation by OPCS Code









Due to small number suppression as per HSCIC rules, we have only been able to show activity of 5 or above. However the majority of activity is shown in the above listed years. For the total numbers please review overall number slide.

Codes used to identify the FESS & Balloon approach is Y76.1 & Y40.3

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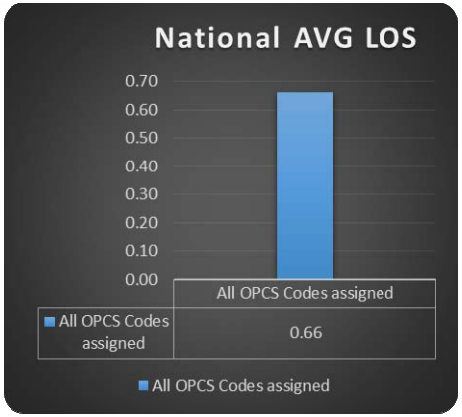
Activity Levels for all OPCS Codes assigned

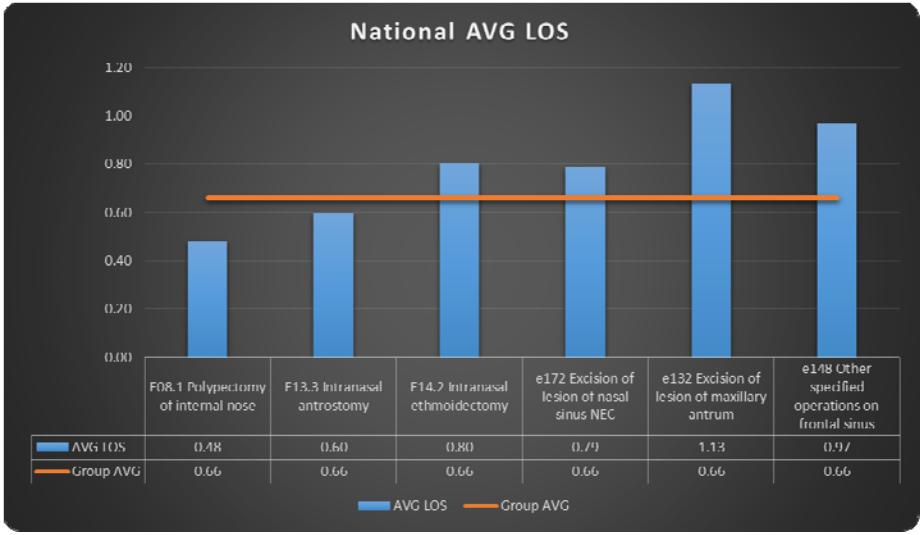
OPCS 4.7 Code	Description	Primary Position	Recorded in Any position
E13.3	Intranasal antrostomy	2487	10320
E14.2	Intranasal ethmoidectomy	2843	8943
E14.8	Other specified operations on frontal sinus	1098	2778
E08.1	Polypectomy of internal nose	6613	9030
E13.2	Excision of lesion of maxillary antrum	520	962
E17.2	Excision of lesion of nasal sinus NEC	349	525
	Total Procedures Performed		32558

It is important to note that in each episode of care, multiple procedures are performed and in some cases up to 7 individual procedures.

Length of Stay Analysis

- Length of stay has been calculated based on the primary procedure coded in the episode. Due to the prevalence of multiple procedures, this will have an impact on the LOS. However on average there are 2.75 procedures per episode.





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Length of Stay Analysis % Split

E172 - Excision of lesion of nasal sinus NEC

LOS Days	Count of episodes	% Split
0	294	56.00%
1	187	35.62%
2	17	3.24%

E133 - Intranasal antrostomy

LOS Days	Count of episodes	% Split
0	1609	64.70%
1	767	30.84%
2	58	2.33%
3	14	0.56%
4	12	0.48%

E148 - Other specified operations on frontal sinus

LOS Days	Count of episodes	% Split
0	620	56.47%
1	373	33.97%
2	34	3.10%
3	15	1.37%
4	12	1.09%
5	8	0.73%
6	6	0.55%
7	7	0.64%

E142 - Intranasal ethmoidectomy

LOS Days	Count of episodes	% Split
0	1639	57.65%
1	1091	38.37%
2	54	1.90%
3	22	0.77%
4	14	0.49%

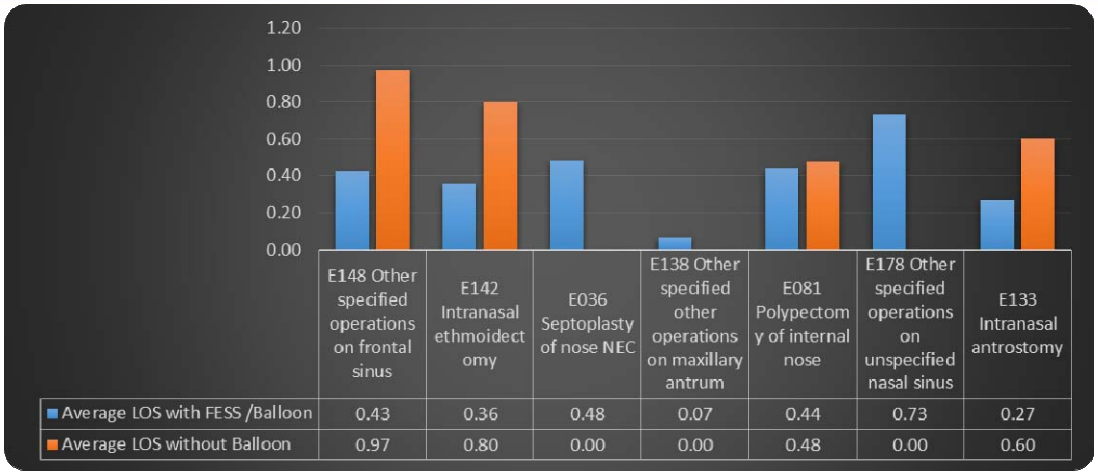
E132 - Excision of lesion of maxillary antrum

LOS Days	Count of episodes	% Split
0	285	54.81%
1	190	36.54%
2	16	3.08%
3	11	2.12%

E081 - Polypectomy of internal nose

LOS Days	Count of episodes	% Split
0	4070	61.55%
1	2325	35.16%
2	137	2.07%
3	44	0.67%
4	16	0.24%
5	7	0.11%

Length of Stay – FESS & Balloon Episodes



** Please note if LOS is 0, then no data is available*

Primary Procedure	Average LOS with FESS /Balloon	Average LOS without Balloon	Count of Episodes	Max LOS With Balloon	Min LOS with Balloon
E148 Other specified operations on frontal sinus	0.43	0.97	145	11	0
E142 Intranasal ethmoidectomy	0.36	0.80	47	2	0
E036 Septoplasty of nose NEC	0.48	NA	29	1	0
E138 Other specified other operations on maxillary antrum	0.07	NA	29	1	0
E081 Polypectomy of internal nose	0.44	0.48	16	3	0
E178 Other specified operations on unspecified nasal sinus	0.73	NA	15	2	0
E133 Intranasal antrostomy	0.27	0.60	11	1	0

Source of data HSCIC – Period Apr 13 to Mar 14

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National 18 week Analysis Mar-14 vs Mar-15

- At present the national picture for 18 weeks for ENT is as follows:-

212,949 Patients awaiting ENT Surgery

Data as at March 2015

2,432 Patients waited longer than 18 weeks for ENT Surgery

84% vs 90% target for admitted patients

Target 90%

Description	Total Admitted Patients	Total Within 18 weeks	% within 18 weeks	Total Potential National Fine £
Mar-14 ENT	16,993	14,944	87.9%	£139,880.00
Mar-15 ENT	16,541	13,896	84.0%	£396,360.00

Target 92%

Description	Total waiting List	Total within 18 weeks waiting list	% within 18 weeks	Total Potential National Fine £
Mar-14 ENT	212,949	199,282	93.6%	£ -
Mar-15 ENT	202,440	190,882	94.3%	£ -

Tariff Matrix

Tariff Analysis	CZ14Y 14/15	CZ14Y 15/16	CZ14V 14/15	CZ14V 15/16
Tariff	£1,491	£1,398	£1,491	£1,463
Type	Combined	Combined	Combined	Combined
Trim Point	>5 = £235	>5 = £218	>5 = £235	>5 = £218
AVG MFF	18%	18%	18%	18%
AVG Reference Cost	£1,381	£1,381	£1,340	£1,340

All tariff figures extracted from HSCIC tariff 2014/15 & 2015/16 tariff documents. Also reference costs are associated to the case mix of a CZ14. Therefore this is covering all procedures associated with the HRG code.*

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