External Assessment Centre report

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Assessment report: The XprESS Multi-Sinus Dilation System for the treatment of chronic rhinosinusitis

Document cover sheet

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

Produced by: Newcastle upon Tyne Hospitals (NUTH) and York Health Economics Consortium (YHEC) External Assessment Centre (EAC).

Authors: Michelle Jenks

Iain Willits

Emily Eaton Turner

Mick Arber

Helen Cole

Joyce Craig

Andrew Sims

Correspondence to: Michelle Jenks

York Health Economics Consortium

Enterprise House
University of York
YORK
YO10 5NQ
Tel: 01904 323620
Email: michelle.jenks@york.ac.uk

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

BNF	British National Formulary
BREATHE	Balloon REmodeling Antrostomy THErapy
CADTH	Canadian Agency for Drugs and Technologies in Health
CCA	Cost-consequence analysis
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CKS	Clinical Knowledge Summaries
CPAP	Continuous positive airway pressure
CRS	Chronic rhinosinusitis
CSF	Cerebral spinal fluid
CSS	Chronic Sinusitis Survey
CT	Computer tomography
DSA	Deterministic sensitivity analysis
EAC	External assessment centre
ENT	Ear, nose and throat
ESS	Endoscopic sinus surgery
FESS	Functional endoscopic sinus surgery
GP	General practitioner
HES	Hospital episode statistics
HTA	Health technology assessment
ICS	Intranasal corticosteroid
ICTRP	International Clinical Trials Registry Platform
IFU	Instructions for use
IQR	Interquartile range
ISD	Information services division
ITT	Intention-to-treat
MDD	Medical Devices Directive
MTEP	Medical Technologies Evaluation Programme
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NUTH	Newcastle upon Tyne Hospitals
OTC	Over-the-counter
PICO	Population, intervention, comparator, outcome
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QoL	Quality of life
RARS	Recurrent acute rhinosinusitis
RCS	Royal College of Surgeons
RCT	Randomised controlled trial
RELIEF	HealthcaRE UtiLization and outcomes of FInESS Treatment on the Office
REMODEL	Randomized Evaluation of Maxillary antrostomy versus Ostial Dilation Efficacy through Long-term follow-up
RSDI	Rhinosinusitis Disability Index

RSI	Rhinosinusitis Symptom Inventory
SD	Standard deviation
SNOT-20 or 22	Sino-Nasal Outcome Test (20 or 22 item)
US	United States of America
VAS	Visual analogue scale
WHO	World Health Organisation
WLQ	Work Limitation Questionnaire
WPAI	Work Productivity and Activity Impairment
XprESS MSDS	XprESS multi-sinus dilation system

1 Summary

Scope of the company's submission

The decision problem described by the company in their submission was largely consistent with the scope described by the National Institute for Health and Care Excellence (NICE) with some minor deviations [1]. In terms of population, the evidence presented matched the scope but the EAC was concerned about generalising the results from selected patients enrolled in United States of America (US) trials to the general patient population treated in the NHS. For the intervention, the company included the predecessor technology to the XprESS multi-sinus dilation system (XprESS MSDS) - the FinESS system, with the assumption of equivalence; however, there was only weak indirect evidence to substantiate this. For the comparator, the company did not provide any data on alternative balloon systems currently used within the NHS. This was appropriate given that no data were available on other systems. The company provided data from studies for most of the clinical outcomes specified in the scope; however, published evidence on some key healthcare system resources were not available, requiring the company to use expert advice. There was also no published evidence on use of XprESS MSDS in patients presenting with chronic rhinosinusitis (CRS) with or without nasal polyps.

Summary of clinical evidence submitted by the company

The company performed an adequate literature search and sift using inclusion and exclusion criteria consistent with the scope. The company identified 6 studies described in 10 published papers from its search of databases. One of the 10 papers included a meta-analysis. These were supplemented by an additional 3 studies that the company identified internally; 2 of these studies were reported as abstracts only and 1 study was reported as a non-peer reviewed white paper.

The only experimental comparative evidence included by the company was the Randomized Evaluation of Maxillary antrostomy versus Ostial Dilation Efficacy through Long-term follow-up (REMODEL) non-inferiority randomised controlled trial (RCT), which compared balloon dilation (XprESS MSDS or FinESS system) with functional endoscopic sinus surgery (FESS). The methodology of this study and the first 6 months follow-up were published in a paper by Cutler *et al.* (2013) [2]. This was supplemented by the papers by Bikhazi *et al.* (2014) reporting follow-up at 12 months [3] and Chandra *et al.* (2016) reporting follow-up at 24 months, which also included an enlarged cohort compared with previous papers [4]. The primary outcome of the

REMODEL trial was change in Sino-Nasal Outcome Test (SNOT-20) score which is a disease specific quality of life (QoL) tool for CRS. This outcome, was pre-specified in the trial protocol in www.clinicaltrials.gov, but the secondary outcomes were not [5].

The REMODEL trial reported statistically significant and clinically important improvements in SNOT-20 score in both the balloon dilation arm (-1.67±1.10 [SD]) and the FESS arm (1.60±0.96) [2] in patients (n=92) with uncomplicated CRS, associated with maxillary sinus disease with or without anterior ethmoid disease. There were no statistically significant differences between the treatment arms at any time point, except at 1 week where there was a greater (but not clinically important) reduction in favour of XprESS. The significant improvements in SNOT-20 score were rapid (occurring after 1 week) and persisted for at least 2 years [4]. There were no significant differences between balloon dilation and FESS reported in the secondary outcomes of ostia patency, subsequent rhinosinusitis episodes, work productivity and activity, complications, and requirement for revision treatment. There was a statistically significant difference reported in requirement for subsequent nasal debridement in the balloon arm compared with FESS (0.1 versus 1.2; $p<0.001$). Additionally, there was evidence that balloon dilation was associated with patient benefits such as improved recovery time and reduced requirement for analgesia compared with FESS.

The company's submission also included 3 published single armed observational studies of the XprESS MSDS that reported post-procedural outcomes compared with baseline (pre-procedural). These were the XprESS multi-sinus registry study [6], the XprESS registry [7], and the XprESS maxillary pilot study (white paper) [8]. Additionally, the company included the published HealthcaRE UtiLization and outcomes of FInESS Treatment on the Office (RELIEF) study [9] and the Balloon REmodeling Antrostomy THErapy (BREATHE) study [10-12] which used the FinESS system as the intervention. A published meta-analysis of these studies [4], which additionally included data from the unpublished FinESS registry [13], but excluded the XprESS registry [7] (because it largely reported on hybrid surgery) was also described.

The observational studies provided supplementary longitudinal data that were largely consistent with the results reported in the REMODEL trial. The data showed that balloon dilation was associated with significant improvement in QoL and improvements in symptoms compared with baseline. These benefits appeared to be rapid (appearing after 1 week) and relatively long-lasting (up to 2 years). The XprESS multi-sinus study provided evidence, through subgroup analysis, that the XprESS MSDS was effective in the maxillary, frontal and sphenoid sinuses.

Summary critique of clinical evidence submitted by the company

The EAC replicated the company's literature search and identified the same number of papers for sifting. The EAC performed an additional broader literature search which did not identify any additional studies with unique patients that were consistent with the scope. The EAC excluded the retrospective study by Eloy *et al.* (2012) [14] included by the company on the basis that it investigated the wrong population (surgical revision). Thus the EAC is confident that all relevant studies were included.

The EAC considered that the REMODEL trial [2-4], being the only experimental comparative study identified, was the pivotal source of clinical evidence to support the company's submission. The EAC considered that this study exhibited relatively high methodological quality, with appropriate randomisation and concealment of allocation and reporting a relevant pre-specified primary outcome (SNOT-20 score) with suitable statistical analysis. This reduced the risk of selection bias and reporting bias. As blinding was not feasible and a subjective primary outcome was selected, there was a moderate to high risk of performance bias. However, the EAC was most concerned by the high dropout rate exhibited in the FESS arm before surgery, which caused the loss of randomisation and the need for analysis according to the protocol used (rather than the preferable *intention-to-treat* [ITT]) analysis. In the opinion of the EAC, this diminished the internal validity of the trial. An additional limitation was the reduced number of patients analysed at later follow-up (for instance n = 25 at 24 months) which increased uncertainty in the outcomes and that it was set in 10 centres in the US.

The EAC also had reservations about the external validity (generalisability) of the trial in its application to the NHS. The following issues were identified:

- Whether the population sampled in the REMODEL trial was representative of treatments undergoing surgical intervention in the NHS (in particular, variance in clinical care pathways and service delivery arising from the differences in the US and English settings).
- Definition of "maximal treatment" in the trial compared with NHS practice.
- The lack of data provided on patients with nasal polyps compared with those without.
- Possible differences in efficacy and safety of the XprESS MSDS and the FinESS system, which were assumed equivalent with only weak indirect evidence to support this assumption.

The EAC considered that in general, longitudinal data from the observational studies supported the results of the REMODEL trial, with the same caveats as described. Overall the data showed that in a selected patient population, the use of balloon dilation is associated with non-inferior QoL improvements compared with FESS, and this effect is immediate and continues for at least 2 years. The evidence also showed that balloon dilation is associated with improved patient recovery times and reduced requirement for analgesia. However, the EAC considered that the finding that XprESS MSDS is associated with reduced requirement for subsequent nasal debridement compared with FESS was not generalisable to the NHS. Thus, although overall the company's claims of clinical equivalence with FESS are plausible, these results should be considered in the context that there is some uncertainty concerning their applicability to the NHS.

Summary of economic evidence submitted by the company

The company identified 6 studies that met its selection criteria for economic studies considering balloon sinus dilation using the XprESS Multi-Sinus Dilation System or equivalent. All provided evidence on balloon dilation systems manufactured by other companies, for example Acclarent. None of these systems are currently used in the NHS. Hence the EAC judged all the studies to be out of scope and therefore identified no relevant health economic studies.

The company provided the EAC with a *de novo* economic model, written and executed in Microsoft Excel. The model adopted a decision tree structure (capturing 1st year costs) followed by a Markov model with 2 health states (capturing costs in years 2 to 5). The cycle length of the Markov model was 1 year. The population within the model was average patients attending for CRS surgery, where multiple sinuses are treated within 1 episode of care. The company compared the XprESS MSDS to 2 comparators, FESS and treatment with the Acclarent balloon dilation system. The decision tree simulated patients on a pathway who had an absolute risk of requiring a follow-up GP appointment, being readmitted to hospital or requiring revision surgery. In the decision tree, the following outcomes were included: initial surgery, GP visit, readmission, pain management, revision surgery. The model captured the number of patients at each endpoint and the cost of that outcome to determine the year 1 costs. The Markov model element of the model had 2 health states: surgery revision and surgery success. Again the model captured the number of patients in each state and the cost of being in that state (GP visit, revision surgery) to determine the costs in years 2 to 5. To populate its economic analysis, the company utilised data from 2 key sources: the REMODEL study [4], and a national audit [15] in addition to advice from

UK clinical experts. The inputs for surgical health states under general and local anesthetic, GP follow-up, readmission and revision, and surgery success were referenced to relevant clinical studies and expert opinion. Values for unit costs were obtained from national datasets.

The company reported that, in the base case, the introduction of XprESS MSDS would lead to estimated cost savings to the NHS of £1,302 per patient over a 5 year time horizon compared with FESS (cost per patient of £2,679 in XprESS MSDS arm and £3,981 in FESS arm). Univariate sensitivity analyses and multi-way scenario-based sensitivity analyses were conducted around all model inputs, which showed the results of the company's analysis to be robust within the ranges examined. Break-even analyses were conducted varying the procedure time with XprESS and procedure time with FESS. The company reported that XprESS was cost-neutral when the procedure time with XprESS was 80 minutes or cost-saving when the procedure time with FESS was above 41 minutes.

Summary critique of economic evidence submitted by the company

The EAC performed a literature review for economic studies comparing XprESS MSDS (including its predecessor, the FinESS system) to FESS and other balloon systems used within the NHS. No relevant health economic studies were identified by the EAC.

The EAC's critique of the model found it was easy to navigate and replicate and the company's description of the model, inputs and results were generally clear. The EAC identified several strengths of the analysis including that:

- The model matched the scope of the decision problem as well as possible, given the available evidence.
- XprESS MSDS was compared with 1 of the comparators listed in the scope (FESS) and the company attempted to make a comparison to other balloon dilation systems used within the NHS by making a comparison to a balloon dilation system previously used within the NHS (Acclarent). The Acclarent device was withdrawn from the UK market on 31st December 2015 (see correspondence log, appendix 3).
- The model structure, a decision tree followed by a Markov model, using an NHS perspective was appropriate for the decision problem.
- The company applied health care system outcomes within the model as specified by the scope. All other outcomes were appropriately assumed to be consistent between the 2 treatment options.

- Discounting was applied within the model to those costs incurred in the future.

- Clinical evidence was taken from the REMODEL study, which represents the best available clinical data on XprESS MSDS [4]. Relative risks were calculated from this RCT and applied to national audit data to generate results that the company argued were more specific to the NHS [15].

- Resource use and unit costs were in general appropriate. Verification of model inputs from clinical experts was sought where published evidence was scarce.

- Extensive deterministic sensitivity analyses were conducted to explore the impact of parameter uncertainty within the model. Structural uncertainty was addressed through consideration of different model time horizons.

The EAC considered there to be a number of weaknesses with the input parameters used within the company's model, some of which have a material impact on the results of the model:

- Revision surgery was assumed to occur more frequently in patients treated with FESS than with XprESS MSDS. Based on expert advice and published evidence the EAC has judged that modelling a difference in revision surgery in years 2-5 is not supported by the current evidence base.

- Clinical data derived from the REMODEL study [4] was assumed to generalise to NICE's decision problem. There are potential differences between the population in the REMODEL study and the population described in the scope (see Section 3.5.3), since the study was set in the US. The study also used a mix of devices and had a high dropout rate, creating attrition bias.

- The company carried out bottom-up costing to determine the cost of each procedure under general anaesthetic. The EAC sought to verify the company's assumptions on the resource used to inform the costings by asking its clinical experts. However, there were material differences of opinion between the company's and EAC's experts on key inputs such as surgery duration and length of hospital stay. Adopting the different estimates materially changed the model's results. In view of this uncertainty, the EAC undertook a structured literature search which identified 3 sources of estimates for the key variable of procedure time [15-17]. All 3 estimates were similar to the value used by the EAC,

providing increased certainty for the value provided by the EAC's experts.

Minor weaknesses of the analysis included an inconsistent cost year throughout the model adopted for parameters and an absence of rationale for not undertaking probabilistic sensitivity analysis (PSA); however, the exclusion of this analysis was not a limitation in this case. The company did not make a comparison between XprESS MSDS and other balloon systems currently available within the NHS, nor did they carry out subgroup analyses. The EAC judged that this was warranted given a paucity of data to inform these analyses.

External Assessment Centre commentary on the robustness of evidence submitted by the company

The clinical evidence submitted by the company comprised 6 studies, all consistently showed benefit, particularly in terms of improving quality of life, from using XprESS MSDS compared to baseline, and in the RCT [4] compared to FESS. None showed evidence of harm. It thus supported the company's claim that balloon dilation was non-inferior to FESS in terms of the primary outcome (measurement of QoL using the SNOT-20 score). Furthermore, the evidence showed that balloon dilation offered other advantages over conventional FESS by speeding recovery, reducing post-operative pain and reducing the requirement for nasal debridement. The submitted clinical evidence comparing XprESS MSDS with FESS is considered to have internal validity for the populations included in the studies.

All clinical studies, however, were set in the US and in selected patient populations. These give rise to concerns around the generalisability of the results to the NHS. Specifically, there is uncertainty regarding whether the patients enrolled had comparable refractory CRS with patients undergoing surgery in the NHS. Furthermore, the impact of nasal polyps on treatment effect and the comparative efficacy of balloon dilation for patients with more complex sinus disorders were not explored within the evidence base. Up to two thirds of patients presenting to secondary care with CRS have nasal polyps [18].

The economic evidence submitted by the company built upon the clinical data, specifically the REMODEL study [4] and was therefore subject to the same generalisability issues. The company modelled clinical data from a national audit of surgery for nasal polyposis and CRS in 87 hospitals in England and Wales during a 6-month period in 2000 [15]. This was supplemented by advice from its UK experts and national cost databases to populate its

economic model. The reliance on clinical experts, whilst necessary, also gives rise to uncertainties about input validity.

Overall, the EAC considers that whilst the evidence submitted by the company was largely internally valid, it will not generalise to all people with chronic rhinosinusitis, including recurrent acute rhinosinusitis, in whom all medical therapy has failed within the NHS. Rather, the clinical evidence is robust in a subgroup of this population, likely those with less severe CRS and without severe nasal polyposis. The results from the economic model are uncertain because of the need to use expert advice to inform key parameters.

Summary of any additional work carried out by the External Assessment Centre

The EAC conducted a cost-consequence analysis (CCA) comparing XprESS MSDS with FESS using the company's model with updated input parameters. This changed the direction of the savings with XprESS MSDS incurring costs of £330 per patient versus FESS (cost per patient of £1,694 in the XprESS MSDS arm and £1,364 in the FESS arm). The EAC conducted univariate sensitivity analysis around all model input parameters to determine the key drivers of the analyses. The EAC varied each input by ±20% and presented the results in a tornado diagram. The direction of the model's result was not sensitive to varying any of the inputs by ±20%. The results were sensitive to the cost of each procedure, with the change in direction of results from the company's to the EAC's base case largely due to a reduction in the cost of FESS procedures. This cost was reduced by the EAC based on expert advice and published sources including audit data which reported a shorter duration of FESS than that used by the company [15-17].

A series of scenario analyses were conducted by the EAC. The results of these analyses are shown in Table 1.1.

Table 1.1: Summary of EAC's scenario analyses

Scenario	Cost saving per patient* (base case = -£330)
Length of stay data from hospital episode statistics (HES) used in both arms	-£136
XprESS MSDS procedures conducted under local anaesthetic take place in an outpatient setting	-£308 where 10% of procedures are under local. -£140 where all procedures are under local
Cost of procedures under local anaesthetic derived though company's ratio	-£311
Rate of revision in years 2-5 estimated from national audit for both arms [17]	-£363
Hospital appointment for debridement for FESS patients	-£137
Hospital appointment for debridement for FESS patients and a proportion of XprESS MSDS have procedure in an outpatient setting	Break even where 80% of XprESS MSDS patients are treated as outpatients
Proportion of patients visiting GP equal in both arms	-£346
* A negative value indicates that XprESS MSDS is cost incurring versus FESS	

In all but 1 of the scenarios presented in Table 1.1, XprESS MSDS remained cost incurring versus FESS. The scenario that generated cost savings required all FESS patients to have an additional hospital visit for debridement and over 80% of XprESS MSDS patients undergoing their procedure under local anaesthetic as an outpatient. The EAC understands, based on expert advice, that there is variability in the practice of routine debridement following FESS. In Trusts where this is conducted and where the majority of XprESS MSDS procedures are carried out in an outpatient setting, there is the potential for cost savings to be generated. However, the majority of the EAC's analyses suggest that XprESS MSDS is not likely to offer cost savings within the NHS based on the identified estimates of FESS procedure time. There does, however, remain uncertainty around this parameter and other key drivers of the model, namely the duration of hospital stay following each procedure. Further research would be required to address this uncertainty and allow firmer conclusions to be drawn.

2 Background

2.1 Overview and critique of company's description of clinical context

2.1.1 Critique of company's description of clinical context

The company provided a brief overview on the definition, pathology, prevalence and impact of chronic rhinosinusitis (CRS) in Section 3.1 of its submission. The External Assessment Centre (EAC) agrees with the factual content of this section and has cross-referenced the information to confirm its veracity.

In Sections 3.3 to 3.10 of the submission, the company described the current pathways in the management of CRS and how they might be altered should the XprESS multi-sinus dilation system (XprESS MSDS) be adopted. The EAC did not fully agree with all the content of these sections and identified the following issues (mainly concerning Section 3.3, Clinical pathway of care).

In Section 3.3 of the submission, the company stated "functional endoscopic sinus surgery (FESS) or balloon dilation is commonly performed". The EAC considered that currently in the NHS, FESS is the main surgical intervention of choice, with balloon dilation not performed in all NHS trusts. Where balloon dilation is used, it tends to be performed in a selected group of patients (correspondence log, appendix 1, collated responses, page 14).

- Concerning FESS, the company stated "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". The EAC considered that this was not representative of practice in the NHS, with 3 out of 4 of the EAC's clinical experts stating this is not performed routinely following FESS, and the fourth expert stating that a single debridement after 1 week is performed. The correct use of saline rinses should preclude the need for nasal debridement in most patients (correspondence log, appendix 1, collated responses, page 21). This statement was repeated in Section 3.4 of the company submission.

- The company stated "Complications associated with balloon dilation are theoretically similar to those associated with FESS; however, they occur less often". The EAC noted this statement was not referenced. In the 1 comparative study [2], balloon dilation was associated with a statistically significant lower rate of postoperative nasal bleeds but other complications were low and similar in both arms (see Section 3.7 of this document.)

- In Section 3.4, the company stated “After FESS, patients usually return to normal daily activities within 7 to 14 days”. The EAC considered that this statement was not evidenced in this section, and is higher than the 4.8 ± 6.2 (SD) days for FESS reported in the REMODEL study [2]. However, an estimate of 1 to 2 weeks off work was estimated by most the EAC’s clinical experts (correspondence log, appendix 1, collated responses, page 19).

- In Section 3.5, the company stated “In contrast to FESS, balloon sinus dilation is easily performed under local anesthesia in a day theatre setting”. The EAC noted that feedback from the clinical experts indicated that, in the NHS, balloon dilation is usually performed in an operating theatre with general anaesthesia, in the same way as FESS is performed. Further, hybrid surgery will be conducted within an operating theatre. This accounts for about half of all operations using balloons (correspondence log, appendix 1, collated responses, page 16). Both FESS and balloon dilation are typically performed as day cases (correspondence log, appendix 1, collated responses, page 19).

The EAC noted that throughout the background, the company did not describe the pathophysiology or diagnosis of CRS with nasal polyps, which occurs more frequently than CRS without polyps. This distinction is important because it impacts on choice of medical and surgical management (see Section 2.1.2).

2.1.2 EAC’s description of clinical context

Guidelines relevant to UK practice

The National Institute for Health and Care Excellence (NICE) has produced Interventional Procedure Guidance (IPG 273) on “Balloon catheter dilation of paranasal sinus ostia for chronic sinusitis” [19]. This guidance, produced in 2008, predates the launch of XprESS MSDS and most of the evidence for balloon dilation for CRS. NICE Clinical Knowledge Summaries (CKS) have produced guidance for healthcare professionals for the management of sinusitis in primary care [20], but this does not give recommendations for secondary care management (including surgical options).

The clinical experts advised the most important guideline on CRS informing NHS practice is the “European Position Paper on Rhinosinusitis and Nasal Polyps (2012) [21]. This evidence-based guideline describes patient pathways from primary to secondary care and includes recommendations on balloon dilation. The “Commissioning guide: rhinosinusitis” by ENTUK and the Royal College of Surgeons (RCS) [22] provides additional UK specific guidance on the management of acute rhinosinusitis and CRS in primary and secondary

care. These guidelines are NICE accredited; however they do not address the use of balloon dilation for CRS.

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses. Episodes of the disease lasting 12 weeks or less are categorised as acute rhinosinusitis, and longer episodes are classed as CRS. Acute sinusitis usually has an infective aetiology. The aetiology of CRS is more complex and likely to be multifactorial, with inflammation, infection and obstruction of sinus ventilation (blockage of sinus entrances) contributing to the pathology. A third classification of rhinosinusitis, recurrent acute rhinosinusitis (RARS), refers to frequent episodes of symptomatic rhinosinusitis that requires long-term management similar to CRS [21, 22]. An important additional factor to the classification of CRS is the presence or absence of nasal polyps. These are freely movable non-tender polypoidal masses arising mainly from the mucous membranes of the nose and paranasal sinuses that can obstruct the ventilation of the sinuses.

Symptoms of CRS include nasal blockage, obstruction, and congestion or nasal discharge, accompanied by facial pain or feeling of pressure, and loss or reduction in the sense of smell (anosmia). The use of a nasal endoscope may reveal nasal polyps; mucopurulent discharge primarily from middle meatus; and/or oedema/mucosal obstruction primarily in middle meatus. Computed tomography (CT) may reveal opacification with mucosal changes within the ostiomeatal complex and/or sinuses [21]. However, CT scans are not used in the diagnosis of CRS other than as a rule out test.

The prevalence of CRS in Europe and North America has been estimated to be between 6% (physician led diagnosis) and 11% (patient led diagnosis) [23]. Up to two thirds of patients presenting to secondary care with CRS have nasal polyps [18]. Both CRS and RARS are debilitating diseases that have a high negative impact on patient quality of life (QoL) and pose a large financial burden to the NHS [23].

NHS patient pathways in England

Primary care

Chronic sinusitis is usually diagnosed in primary care when 2 or more symptoms persist for at least 12 weeks, 1 of which should be either:

- Nasal obstruction and/or nasal discharge.
- Facial pain/pressure or anosmia.

The presence of allergic rhinitis and asthma should be considered and treated accordingly. Anterior rhinoscopy should be used to identify nasal polyps and to exclude sinister pathologies. Severity of symptoms should be assessed using a visual analogue scale (VAS) [22].

Treatment for all patients in primary care is symptomatic and primarily consists of saline irrigation and intranasal corticosteroid (ICS). For patients with visible nasal polyps, a course of oral corticosteroids may be considered before ICS. Patients should be reassessed after 3 months and treatment can be continued if symptoms are mild. Referral to an ear, nose and throat (ENT) specialist should be considered in the following instances [20]:

- Frequent recurrent episodes of acute sinusitis which are troublesome (such as more than 3 episodes requiring antibiotics in a year).
- Unremitting or progressive facial pain.
- Nasal polyps which are causing significant nasal obstruction.
- Trial of ICS for 3 months which has been ineffective.

Secondary care

In secondary care, a full history and examination should be undertaken to assess causes and comorbidities. This should include endoscopy but CT is not required unless there is diagnostic doubt or where malignancy or serious complications are suggested. Patients' QoL should be assessed using the SNOT-22 scale (see Section 2.3.4) [22].

Medical treatment in secondary care is maximal to prevent the need for surgery where possible. Treatment from primary care will typically continue with the addition of oral corticosteroids (in patients with nasal polyps) and oral antibiotics (doxycycline or macrolides). Patients will typically be reviewed after 3 months of maximal medical treatment [22].

If moderate or severe symptoms persist after 3 months (VAS score > 3, total SNOT-22 score > 20) then surgery (usually FESS) will be considered following a mandatory CT scan (to assess anatomy and consider alternative pathology if Lund-Mackay score is less than 4). Surgery should only be undertaken with the full informed consent of the patient (for instance, after discussion of the risks and benefits). There is no specific guidance on the type and extent of surgery to be undertaken, with the commissioning guide stating "There is insufficient evidence to inform as to the optimum extent of surgery, instrumentation to be used, or post-operative packing materials" [22]. It has

been estimated through analysis of HES from 2012 to 2013 that around 40,000 sinonasal operations are performed each year in the NHS [23].

Patients should be offered post-operative care as an essential part of their recovery; typically this will involve continued use of saline douches and ICS. It is thought that surgery allows for improved access of local drugs to their site of action and thus improves their efficacy [24].

Mechanism of action

FESS was first developed in the mid-1980s as a less invasive alternative to conventional open surgery [25]. The principal purpose of FESS is to re-establish ventilation and enhance mucociliary clearance of the sinuses. This is achieved through endoscopic removal of diseased tissue, including in the anterior ethmoid sinus, sphenoid sinus, maxillary sinus, and middle meatus. As a minimally invasive surgery, FESS is intended to lessen patient discomfort by reducing trauma. It causes minimal morbidity and bleeding compared with conventional open treatment.

Balloon dilation is also a minimally invasive treatment with the principal aims of improving sinus ventilation and mucociliary clearance. Unlike FESS, balloon dilation does not excise or debulk soft tissue. Instead, the balloon is inflated under high pressure and this causes displacement and microfracturing of the bony lamina surrounding the entrances to the sinuses, such as the maxillary ostia. The subsequent remoulding of the bone results in improved sinus drainage with minimal disruption to the mucosal lining [26]. As the soft tissue is relatively unaffected, reduced patient discomfort and quicker recovery times compared with FESS are claimed [26].

Clinical evidence for surgical intervention

The use of FESS in the NHS in patients with and without nasal polyps was investigated in an audit published in 2003 [15]. It found at 3 months post-procedure that FESS was associated with a “large” effect size reduction (SNOT-22 effect size reduction of 0.81, see Section 2.3.4) in patients with CRS. The effect size was largest in patients who also underwent nasal polyp procedures (0.9) compared with those who only underwent sinus surgery (0.64). At 12 months follow-up, although still significantly reduced from baseline, there was a statistically significant reduction in this effect, for a mean effect size reduction of 0.7 (0.81 for people with polyps and 0.56 for those without).

Results from 3 randomised control trials (RCTs) using FESS (n=212) were synthesised in a Cochrane review [27]. This concluded FESS was a safe surgical procedure but the limited evidence available did not demonstrate it

conferred additional benefit to that obtained by medical treatment in CRS. This was probably due to a lack of evidence rather than evidence of no effect. A limitation of the RCTs included in the Cochrane review was the lack of a suitable placebo control arm or arm of patients using maximal medical treatment [21].

A recent prospective, controlled observational study enrolled 180 patients who received continued maximal medical management or FESS according to their patient preference and/or the clinical recommendation of the treating physician [28]. The study reported that patients receiving FESS had significantly improved QoL as measured using Rhinosinusitis Disability Index (RSDI) and Chronic Sinusitis Survey (CSS) compared with those receiving medical treatment. Additionally they used less on-going medication. Whilst this study was not randomised and therefore potentially subject to confounding, it does suggest that FESS is associated with improved outcomes compared with continued medical treatment.

2.2 *Overview of company's description of ongoing studies*

The company identified 1 unpublished clinical study of the XprESS MSDS. This was a study in children with CRS by Soler *et al.* (2016), the protocol of which was published on clinicaltrials.gov [29] and reported in abstract form as an included study in Section 7.2 of the submission.

The EAC searched the following databases for ongoing studies as part of the additional literature search (see Section 3.1.1 and Appendix 2):

- Clinicaltrials.gov.
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP).
- ISRCTN registry.

From these searches, the EAC identified all the study protocols of the included studies by the company [5, 13, 30-32], including the unpublished study by Soler *et al.* (2016) [29]. The EAC did not identify any additional protocols of studies in progress and is therefore confident that no ongoing studies have been omitted.

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The population was described in Table A1.1 of the submission (Statement of the decision problem) as "People with chronic rhinosinusitis, including recurrent acute rhinosinusitis, in whom all medical therapy has failed". This was the identical to the population described in the scope [1].

The EAC considered the population described in the submission was appropriate. The Instructions for use (IFU) of MSDS state the technology is indicated "To access and treat the maxillary ostia/ethmoid infundibula in patients 2 years and older, and frontal ostia/recesses and sphenoid sinus ostia in patients 12 years and older using a trans-nasal approach. The bony sinus outflow tracts are remodelled by balloon displacement of adjacent bone and paranasal sinus structures".

The EAC noted that the scope and company restricted the population to people with medically refractory CRS. This was appropriate as in practice maximal medical treatment is used before surgery is considered (see Section 2.1.2). The EAC considered that the all studies identified by the company to support the clinical effectiveness and safety of XprESS MSDS included patients that fitted this description, and hence matched the scope of the decision problem. However, the EAC was concerned about generalisability of the results given all the studies were conducted in the US. This gives rise to potential differences between the US and English settings for example in:

- Clinical care pathways and delivery settings.
- Definition of maximal medical treatment.
- Baseline risks for the treated populations.
- Specific indications for FESS and balloon dilation.

The populations included in the clinical studies may also differ from the treated populations in both settings.

As discussed in Section 2.1.2, patients in the NHS are typically only referred to specialists in secondary care after a period of several months. By this time, their condition may be refractory and will not resolve naturally without surgical intervention. In contrast, in the US, patients may bypass primary care and see an ENT specialist sooner, and possibly receive surgery sooner, with a shorter duration of less intense medical management.

According to the clinical experts contacted by the EAC (correspondence log, appendix 1, collated responses, page 12) in England, following referral from primary care, patients will typically undergo maximal medical treatment for a period of about 3 months before surgical intervention is considered. This may include several or prolonged courses of oral antibiotics and also oral corticosteroids (particularly in patients with nasal polyps). However, the maximal treatment of CRS and RARS documented in the REMODEL trial [2] (see Section 3) was more conservative, for instance it did not require the use of oral corticosteroids or prolonged use of antibiotics.

The clinical experts contacted by the EAC who used balloon dilation (correspondence log, appendix 1, collated responses, page 14) were consistent in their responses that this technique is usually reserved for patients with specific indications. This includes patients with isolated sinus disease, particularly of the frontal sinus which can be difficult to operate on surgically with FESS, and patients in whom general anaesthesia is contra-indicated. Patients with extensive sinus disease and patients with nasal polyps are not recommended for treatment with XprESS MSDS (see Section 2.3.6).

Additionally, the clinical evidence (other than the XprESS multi-sinus study [6]) did not include patients with indications other than CRS of the maxillary sinus, with or without anterior ethmoid disease.

The EAC judges that the comparative efficacy of FESS and XprESS MSDS is likely to depend on the type and severity of sinus disease, which makes selection of patients in both clinical trials and real-life practice challenging. The EAC noted that there was a consensus from the EAC's clinical experts that balloon dilation potentially provided better outcomes in patients with early stage or isolated sinus disease (correspondence log, appendix 1, collated responses, page 8), whereas FESS was judged to provide better outcomes in those with more severe disease. This raises the possibility that the effect size seen in the identified evidence, particularly in the REMODEL trial [2] would not be replicated in the patients typically treated with surgery in the NHS. The comparability of patients in the REMODEL trial and those being treated within the NHS is discussed further in Section 3.5.3.

2.3.2 Intervention

The intervention described in Table A1.1 of the submission was the "XprESS Multi-Sinus Dilation System"; this was the same as specified in the scope [1]. The company provided the EAC with current EC certification from BSI, a UK Notified Body, dated 27 October 2015 with expiry date 28 October 2020. The certificate was first issued on 29 October 2010 and shows the manufacturer's

quality assurance system meets the requirements of the Medical Devices Directive (MDD) 93/42/EEC in respect of:

- The design, development and manufacture of sterile balloon dilation catheter systems for treatment of chronic sinusitis.

- Securing and maintaining sterility of sterile accessories.

In the UK, the XprESS MSDS is supplied as the XprESS LoProfile system, which is a single-use standalone device. In the US, XprESS is also available as XprESS Ultra and XprESS pro. The EAC has confirmed with the company that there are no important functional differences between these systems, and that the LoProfile system is the most versatile, with intermediate ball tip sizes and the largest selection of balloons (correspondence log, page 2).

However, some studies identified in the clinical evidence sections of the submission used the predecessor system to XprESS MSDS, the FinESS system. This included the REMODEL RCT [2], which used a mixture of these technologies and did not disaggregate effects. The observational studies used either the XprESS MSDS or FinESS system exclusively.

The company advised the main difference between the systems concerns the approach used to access the sinus, and the types of sinuses that can be treated (correspondence log, page 4):

- The FinESS system has a straight catheter and requires a transantral approach to access the maxillary sinus FinESS. The transantral approach is through a small access hole above the canine fossa (located under the lip) to the maxillary sinus created by the Micro-Trocar of the FinESS system. This is a relatively invasive procedure requiring drilling of the bone. In contrast, the XprESS MSDS uses a trans-nasal approach. This is made possible through the use of endoscopy and because the distal end of the XprESS MSDS is re-shapeable.

- The FinESS system is only indicated for the treatment of the maxillary ostia or infundibula of the anterior ethmoid. In contrast, the flexibility of the XprESS system allows for additional treatment of frontal ostia and recesses, and the sphenoid sinus ostia.

The EAC has been informed by the company that, regarding the action of balloon dilation on the maxillary ostia and ethmoid infundibulum, the 2 systems are functionally equivalent. In Section 5.1 of the submission, the company stated “A review of historical outcome data (Sino-Nasal Outcome Test (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". This suggests to the EAC that the statistician had access to disaggregated data which suggested equivalence in outcome SNOT-20 scores, although this was not verified. This also appears to be consistent with the evidence reported in the meta-analysis of Chandra *et al.* (2016) [4] (see Section 3.8).

In the absence of head-to-head trial data, the EAC assumed the techniques are functionally equivalent for the management of the maxillary and anterior ethmoid sinuses, at least in terms of the primary outcome, the SNOT-20 score. The XprESS system has clear advantages over the FinESS system over its range of application, and would be expected to have more favourable short-term outcomes in terms of patient recovery and comfort, but this cannot be substantiated by evidence from the included trials.

One study identified by the company reported on the use of hybrid surgery, whereby conventional FESS techniques are performed alongside balloon dilation [33]. The EAC has received feedback from the clinical experts and the company that such hybrid surgery is commonly undertaken in practice and the extent of this is highly variable (ranging from simple polypectomy to full sinusotomy). The heterogeneous nature of hybrid surgery makes it difficult to evaluate in terms of both clinical effectiveness and cost. Therefore, for the purposes of this report, only studies reporting standalone balloon dilation have been considered. This is consistent with the scope.

2.3.3 Comparator(s)

The company listed 2 comparators in the statement of the decision problem (Table A1.1 of the submission) which were consistent with the scope [1]. These were:

- FESS.
- Other balloon sinus dilation systems available in the NHS.

In the UK, FESS is the principal surgical option for the management of refractory CRS or RARS, and hence was an appropriate comparator. In the clinical evidence section of the submission, the company identified 1 RCT that compared Entellus balloon dilation with FESS (the REMODEL trial [2]).

The EAC understands that the principal competitor to the XprESS MSDS in the US is the Acclarent balloon system [34]. However, this system was withdrawn from European markets in 2015 [35] and is thus not now available in to the NHS, so is technically out of scope (see correspondence log, appendix 3).

The EAC is aware from its literature searches that there is very little clinical evidence to support the effectiveness or safety of balloon systems other than those manufactured by Entellus Medical or Acclarent. Furthermore, the company did not identify or report any data concerning other balloon systems in the clinical evidence sections of the submission, Therefore, the EAC is satisfied that FESS is the comparator of interest.

2.3.4 Outcomes

The outcomes described in Table A1.1 of the submission are the same as those described in the scope [1]. The principal outcome reported in all the reported studies was change in rhinosinusitis symptoms following surgery as measured by the SNOT-20 scale.

The SNOT-20 is a validated QoL measure that assesses the severity of rhinosinusitis symptoms and their impact on patient wellbeing and function [36]. It consists of 4 domains with a total of 20 questions; the domains are rhinologic; ear and facial; sleep function; and psychological. The patient is requested to score each of the 20 questions from 0 (no problem) to 5 (problem as bad as it can be). Then a mean measurement of these scores is calculated to give an overall score of rhinological symptoms and impact (from a possible minimum of 0 to a maximum of 5). A change in score from baseline of 0.8 or more is regarded as clinically meaningful [36]. Changes in individual domains may also be important in individual patients [37]. An additional measurement of effect size derived from the SNOT-20 is calculated by dividing the mean change score at each post-operative time period by the baseline standard deviation for the relevant group. An effect size of 0.2 is considered small, 0.5 medium and 0.8 or greater is considered large.

The SNOT-22 score is equivalent to the SNOT-20 score except 2 additional questions have been added, concerning nasal blockage, and sense of taste and smell [38]. SNOT-22 scores are reported as the total score per patient, on a scale of 0 to 110 [39]. Only SNOT-20 scores were reported in the evidence identified by the company.

The EAC considered that the SNOT-20 score was an appropriate choice of primary outcome and noted that it has been extensively used in the CRS literature. However, the EAC cautioned that as a QoL measurement the SNOT-20 score was subjective and open to conscious or unconscious bias (see Section 3.5.2). The EAC noted that comparative results for the SNOT-20 were reported within the *de novo* economic model, but were not significantly different, hence the company assumed equivalence within its analysis.

The company included a range of secondary endpoints relating to patient outcomes, healthcare system outcomes, and adverse effects. In general, there was evidence reported to support the patient orientated outcomes, but less evidence to support the healthcare system outcomes, which was important for the economic model. The EAC has interpreted these results in Section 3.6.4 (Table3.6).

2.3.5 Cost analysis

The economic analysis provided by the company, including the *de novo* model, largely matched that of the scope (see Section 4.2). There were 2 deviations from the scope. Firstly, the scope specified FESS and "other balloon sinus dilation systems available on the NHS" as comparators. FESS and Acclarent were included as comparators within the company's economic model. Acclarent was not a relevant comparator given its withdrawal from the UK. Other balloon systems used within the NHS were identified by the company and the EAC's experts but clinical evidence was not identified. The second deviation from the scope was that the company did not model all of the subgroups listed in the scope. The company justified this by stating an assumption that the findings related to an 'average risk' patient and were generalisable to all subgroups.

2.3.6 Subgroups

The statement of the decision problem (Table A1.1 of the submission) was consistent with the scope [1] and listed 6 subgroups which were considered to be of interest. The EAC has considered whether the clinical evidence identified by the company provided useful data on these subgroups:

- "Patients with uncomplicated chronic rhinosinusitis (or uncomplicated recurrent acute rhinosinusitis)". The EAC considered that this subgroup was representative of most the patients included in the identified evidence, and fits the description of patients included in the REMODEL trial [2].

- "Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) with orbital or intracranial involvement". The company clarified in Table A1.1 that no data was provided for this subgroup. The EAC notes balloon dilation is generally indicated for uncomplicated CRS or RARS and that orbital or intracranial complications are contraindications for this procedure.

- "Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) with and without nasal polyps". No results were presented for this subgroup. The EAC considered that the management of this subgroup

was not adequately addressed by the submission for the following reasons:

  - In some studies included in the submission, including the REMODEL trial [2], patients with "gross sinonasal polyposis" were excluded; however, a definition was not provided. Therefore there is uncertainty as to the nature of selected patients in these studies and to what extent they reflect typical surgical case mix in the NHS. About two thirds of patients receiving FESS in the NHS have nasal polyps, with about one third having gross (grade 3) nasal polyposis [15].

  - Only 1 study included in the submission included a comparison of patients presenting with nasal polyps compared to those presenting without nasal polyps. This was the XprESS registry by Brodner *et al.* (2013) [7]. However, this study primarily utilised hybrid surgery (with only 9/175 having received standalone XpreSS MSDS), so was not considered by the EAC to provide relevant evidence.

  - One clinical expert contacted by the EAC confirmed that the presence of nasal polyps would tend to favour FESS over balloon dilation as excision would be required rather than just ventilation (correspondence log, appendix 1, collated responses, page 6).

- The company listed the subgroup "Patients with chronic rhinosinusitis (or recurrent acute rhinosinusitis) affecting the anterior ethmoid sinus in addition to maxillary, frontal or sphenoidal sinus disease". The EAC considered that the majority of the evidence presented by the company was restricted to patients requiring surgery on the maxillary ostia with or without involvement of the anterior ethmoid infundibula, and this included the only comparative data reported in the REMODEL trial [2]. The only evidence of efficacy on other sinuses was provided by subgroup analysis the XprESS multi-sinus study [6]. This was a single-armed observational study and as such was considered by the EAC to be low quality evidence, although it did provide useful data.

- The company listed the subgroup "Patients with anatomic variants such as septal deviations and accessory ostia". The EAC considered this subgroup had been partly addressed by the included studies:

  - The EAC identified 1 study which provided stratified subgroup analysis of patients with mild to moderate septal deviation [33]. However, this study appeared to include the same patients as the

XprESS registry study [7] which mainly utilised hybrid balloon dilation, so was considered out of scope.

- The presence or absence of accessory ostia was partly addressed by the REMODEL trial, which performed subgroup analysis on patients with accessory ostia [2]. No differences in primary or secondary endpoints were observed in this subset of patients.

- Finally, the company listed “Children and young people under 18 years of age” as a subgroup. The company identified data from an unpublished study that was performed in children with CRS [29], but the study was reported as an abstract and thus difficult to interpret and appraise. The company did not otherwise report on the use of XprESS MSDS in children. The EAC noted that the clinical experts were unanimous in their response that in England surgery is rarely undertaken to treat CRS in children (correspondence log, appendix 1, collated responses, page 10).

The EAC has summarised the company’s consideration of the subgroups in Table 2.1.

Table 2.1: EAC summary of the company's consideration of subgroups

Subgroup	Adequately addressed in submission?	EAC comment
Uncomplicated CRS or RARS	YES	Most of the evidence in clinical submission was on this subgroup.
Orbital or intracranial involvement	NO	Subgroup retracted by company in submission.
Nasal polyps	NO	Patients with gross polyposis excluded from studies. No subgroup analysis on patients with nasal polyps in patients receiving standalone XprESS MSDS.
Frontal sinuses Sphenoid sinuses	Partly	One study reported limited subgroup analysis in frontal and sphenoid sinuses, but of low quality.
Anatomic variants (septal deviation and accessory ostia)	Partly	Data identified by EAC on septal deviation not generalisable. Subgroup analysis on accessory ostia performed in REMODEL trial.
Children	NO	Abstract of study in children reported, but unlikely to be generalisable to NHS.

2.4 *Special considerations, including issues related to equality*

The company reported there were no identified equality issues pertaining to the patient population (Section 6.1 of the submission) and the assessment of the technology (Section 6.2 of the submission).

The EAC identified 1 possible equality issue. This concerned people with CRS or RARs who were unable to receive FESS under general anaesthesia because of comorbidities who might be eligible for treatment of their condition with XprESS MSDS under local anaesthesia.

3 Clinical evidence

3.1 *Critique of the company's search strategy*

The Peer Review of Electronic Search Strategies (PRESS) Checklist was used to inform the critique of the company's search strategies [40]. The PRESS checklist is an evidence-based tool used to critically appraise literature search strategies. The PRESS project was funded by the Canadian Agency for Drugs and Technologies in Health (CADTH) and this approach to peer reviewing search strategies is supported by the Cochrane Collaboration's Information Retrieval Methods Group [41].

3.1.1 Search sources

The company searched the 2 sources regarded as the main biomedical bibliographic databases (MEDLINE - via both Ovid and PubMed, and Embase), plus Cochrane Database of Systematic Reviews (CDSR). These 3 sources are core databases where one would hope to find the majority of relevant records for published studies. However, the sources were not in line with the minimum required resources stated in the NICE Company's submission template for clinical evidence and adverse events searches. The Company's submission template states that these searches should include at least MEDLINE, MEDLINE In-Process, Embase, and the Cochrane Library. The last source includes a number of component databases, of which CDSR is just one. Of the other component databases, there is no indication that the company searched Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database and the NHS Economic Evaluation Database (EED). It is not possible to tell from the submission if MEDLINE In-Process has been searched. PubMed contains In-Process records, as do some segments of Ovid MEDLINE. However, by limiting the PubMed searches to just those records indexed with the MeSH heading 'Human' the company has in effect excluded all In-Process records (as In-Process records are not indexed with MeSH). The company does not indicate which segment of Ovid MEDLINE was searched, so it is not possible to be certain if the segment included MEDLINE In-Process. By not searching the resources recommended by the NICE Company's submission template as a minimum for searches of published clinical evidence and adverse effects, the company increased the risk of missed relevant studies.

The NICE Company's submission template indicates that the company should describe the strategies used to retrieve relevant clinical data from unpublished sources. The medical technologies evaluation programme (MTEP) Methods guide indicates that search sources should include registers or databases of ongoing clinical trials, and conference proceedings. There is no indication in

the submission that a search for unpublished studies was carried out (Section 7.1.2 of submission). The 2 unpublished studies referred to in the submission were “identified internally from completed studies by Entellus Medical”. The search sources used for the identification of published studies did include Embase, which does index some conference-related publication types. However, by excluding MEDLINE journals from the Embase search, the company was likely to miss conference abstracts indexed in these journals (as MEDLINE does not routinely index conference abstracts or supplements). The submission methodology would have been enhanced by including a wider search for conference abstracts and by searching key trial registers suggested by methods guidance [42] and research [43], such as ClinicalTrials.gov and the WHO ICTRP. By not searching for unpublished or ongoing studies, the company increased the risk of missed relevant data.

3.1.2 Search strategy structure, search terms and syntax, search restrictions

The reported strategies for Ovid MEDLINE, PubMed and Embase were clearly structured into search concepts. Search terms were grouped appropriately, apart from 1 instance in the PubMed search where the sinuplasty intervention term was grouped with the population terms. Boolean operators were used appropriately. Although the syntax for line combinations is not made explicit in the reported Ovid strategies, result numbers indicate they have been combined correctly. The strategies were mostly constructed using explicitly specified subject headings and free-text searches, apart from the Embase search which did not include free-text search terms for the population concept.

The strategies explicitly included key subject headings for the population and interventions of interest. Some potentially relevant subject headings were not included (for example the MeSH headings Dilatation/ and Catheterization/ in Ovid MEDLINE and PubMed), but the broad approach taken to fields in the free-text search lines (see below) meant that records indexed with these subject headings would have been retrieved anyway.

The strategies included key free text terms for the population and interventions of interest. No spelling errors were identified and the use of truncation was appropriate. In some respects the company took a highly sensitive approach to the free-text searches (i.e. for the intervention concept, searching for all records which included the terms dilat*, balloon* or catheter*). This sensitive approach to the intervention terms would have increased the likelihood of retrieving relevant studies (though at the expense of precision). In some other respects, the range of free text terms, and the way they were used, had some limitations which could have increased the risk

of missed relevant studies. For example, search methodology would have been enhanced by including potential free-text variants for sinusitis (such as sinus disease or sinus infection), by including the free-text terms ‘sinuplasty’, ‘sinusitis’ and ‘rhinosinusitis’ in the Embase search (as they did in the Ovid MEDLINE and PubMed searches), by including the term ‘sinuplasty’ in the intervention group of terms in PubMed, and by including search terms for the device trade name.

The company took a basic approach to the use of search fields for the free-text searches; in Ovid the ‘all field’ (af) and ‘multi-purpose’ (mp) syntax were used, whilst the PubMed search did not restrict by field. Although this approach meant the searcher had less control over the search, and although it was likely to decrease precision, it did also lead to relevant subject headings being covered by the search strategy even when not explicitly included. For example, although the Ovid MEDLINE and PubMed strategies did not explicitly include the relevant MeSH headings of Dilatation/ and Catheterization/ (as referred to earlier), the strategies would have retrieved studies indexed with these headings anyway, through the use of the ‘multi-purpose’ syntax.

The documented searches were restricted to studies published in English. This reflected the study selection criteria, although no rationale for the language restriction was found in the submission. The searches were also restricted to studies published from 2006. Again, no rationale was found in the submission for the date restriction, but it is understood Entellus was founded in 2006 [44]; this being the case the date restriction was appropriate. The approach the company took to limiting the searches to human studies was not optimal, and increased the risk of missed relevant records. By restricting strategies using the ‘Human’ limit (rather than using the standard safer algorithm of results NOT (animals NOT human))) the company risked excluding records which were not fully indexed, or where the indexer had not used the Humans subject heading. The company also restricted the Embase search to just those journals which were not also included in MEDLINE, presumably in order to reduce duplicate records from the 2 databases. In doing so, the company reduced the chance of finding relevant records from these journals using Emtree terms (which are not available in MEDLINE) and increased the risk of missing conference abstracts (as conference abstracts and supplements are not routinely indexed in MEDLINE). A safer approach to dealing with database overlap would have been to de-duplicate all records post-search at record management stage. No study design filter was used; this was appropriate for a search which aimed to retrieve a wide range of study designs and studies which reported on adverse events. The main databases searches were carried out in December 2015 and as such had reasonably good currency at the time of submission.

3.1.3 Re-run company searches

The EAC could not fully reproduce all the company searches as strategies were not reported for the search of CDSR. The Ovid MEDLINE, PubMed and Embase search strategies were re-run as reported. For the purpose of the Ovid MEDLINE search, the EAC assumed that the company searched the following segment: Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE. The Ovid MEDLINE and Embase searches as reported included unbalanced parentheses, but for the purposes of the re-run searches the EAC assumed this was just a reporting error, and these were corrected for the re-run versions. The strategies used when re-running the company's search and the volume of results identified for each search source, are fully reported in Appendix 1. The EAC search identified retrieved 395 records, with 229 unique records remaining after deduplication. This was a similar yield to the original company searches (which retrieved 390 records, with 229 unique records remaining after deduplication).

3.1.4 EAC's additional searches

A *de novo* literature search was undertaken by the EAC. This search aimed to identify evidence on the XprESS MSDS or the FinESS system for treatment of patients with CRS or recurrent acute rhinosinusitis.

A strategy was developed for MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through assessment of the company strategy, discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The approach taken to the search strategy development aimed to balance sensitivity and precision, reflecting the project resource and timelines.

The main structure of the strategy comprised 2 concepts:

- Rhinosinusitis.
- Balloon catheter dilation.

The concepts were combined as follows: rhinosinusitis AND balloon catheter dilation. The strategy also included terms related to the device brand names and manufacturer name.

The strategy excluded animal studies using a standard algorithm. The search was limited to studies published in English as project timelines and resource

precluded the translation of foreign language papers. The strategy was restricted to studies published from 2006 to date. The EAC decided this date was appropriate, given the company was founded in 2006. The search was not restricted by study design.

The sensitivity of the draft MEDLINE strategy was assessed at development stage by checking successful retrieval of the 11 published studies included in the Submission bibliography of selected studies (Submission, Attachment 4). Of the 11 studies, 10 could be found in Ovid MEDLINE and the draft strategy successfully retrieved all.

The final strategy for MEDLINE is shown in Figure 3.1. The final MEDLINE strategy was translated appropriately for the other information resources searched. The PubMed search was restricted to just those records not fully indexed in MEDLINE. The EAC searched all of the resources reported by the company. The EAC also searched additional resources including those resources required as a minimum in the NICE Company's submission template and other sources of published and unpublished evidence (general bibliographic databases, databases of conference proceedings, trial registers and websites). The websites included the manufacturer website (Clinical Data Center Clinical Library page) and EuroScan (a global collaborative network that collects and shares information on innovative technologies in healthcare), plus a selection of additional sites informed by the list of external organisations identified on the NICE final scope document for the technology. The EAC also checked reference lists in relevant studies and reviews which were identified, and formally contacted clinical experts to ask if they knew of any studies which were unpublished, published in abstract form only, or very recent and likely to be published at an upcoming conference.

Strategies (including search dates and interfaces) for all search sources and volume of results returned are included in Appendix 2.

Results of the searches were downloaded in EndNote reference management software. The records were deduplicated using several algorithms, both against each other and against the records retrieved by the re-run company searches.

Figure 3.1: EAC search strategy for Ovid MEDLINE and MEDLINE In-Process

1 exp Sinusitis/ (17489)
2 Paranasal Sinus Diseases/ (4824)
3 sinusit$.ti,ab,kf. (13902)
4 (nasosinusit$ or pansinusit$ or ethmoidit$ or sphenoidit$ or antritis).ti,ab,kf. (643)
5 rhinosinusit$.ti,ab,kf. (5667)
6 ((sinus or sinuses or sinonasal or sino-nasal) adj5 (infection$1 or disease$1 or inflam$)).ti,ab,kf. (7710)
7 (RARS or CRS).ti,ab,kf. (8294)
8 (CRSwNP or CRSsNP).ti,ab,kf. (425)
9 Rhinitis/ (10106)
10 rhinit$.ti,ab,kf. (22259)
11 exp Paranasal Sinuses/ (22994)
12 ((paranasal$2 or nasal$2 or ethmoid$ or frontal$ or maxilla$ or highmore or upper jaw or sphenoid$ or ostia$) adj3 (sinus$ or cavity or cavities or antrum or antrums or mucosa$1)).ti,ab,kf. (44627)
13 (nasal adj3 (inflamm$ or virus$ or bacteri$ or infectio$)).ti,ab,kf. (2944)
14 or/1-13 (96697)
15 Dilatation/ or Dilatation, Pathologic/ (19108)
16 Catheterization/ (47577)
17 (balloon$1 or sinuplast$ or sinu-plast$).ti,ab,kf. (53089)
18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter$) adj5 dilat$).ti,ab,kf. (2151)
19 or/15-18 (108434)
20 xpress$2.ti,ab,kf. (110)
21 finess$2.ti,ab,kf. (797)
22 entellus$2.ti,ab,kf,in. (133)
23 msds.ti,ab,kf. (612)
24 or/20-23 (1652)
25 14 and 19 (680)
26 14 and 24 (4)
27 (xpress$2 multisinus or xpress$2 multi-sinus or finess$2 sinus).ti,ab,kf. (0)
28 or/25-27 (683)
29 exp animals/ not humans/ (4189142)
30 28 not 29 (648)
31 limit 30 to (english language and yr="2006 -Current") (278)
32 remove duplicates from 31 (277)

Key to Ovid symbols and commands

$ Unlimited right-hand truncation symbol

$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,in.	Searches are restricted to the Title, Abstract, Keyword Heading Word, Institution fields
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
or/1-3	Combines sets 1 to 3 using OR

3.2 *Critique of the company's study selection*

The company identified 70 studies from their literature search that required further evaluation through full retrieval of the papers. In addition to this, 3 unpublished studies that were identified outside of the search were included. These were described in Section 7.1.2 of the submission and reported separately; however, 1 of these studies had been published at the time this report was written and was identified by the EAC's subsequent literature search (Section 3.1).

The company sifted the studies identified by the literature search according to the criteria reported in Table B7.1 of the submission. These criteria were in alignment with the scope and were considered appropriate by the EAC. Using these criteria, the company identified all the relevant primary research that had been published on the use of Entellus Medical balloons, as well as systematic secondary research pertaining to this. The population was restricted to people of all ages with CRS, although the EAC noted that patients with RARS were also included. Any or no comparator was allowed, but the studies were required to report clinical efficacy or safety outcomes.

After sifting of the full papers, the company identified a total of 11 separate publications which they considered should be included in the submission. These described 6 studies with unique patients. An additional 2 unpublished studies identified outside of the search by the company were also reported. These were technically included by the EAC, but limited in value as they were provided as abstracts only (see Section 3.3.1). The third paper referred to by the company as being as identified internally was the white paper by Gould *et al.* (2012), also known as the XprESS Maxillary Pilot study [8]. This was clarified following communication with the company (correspondence log, page 21), and took the total of unique studies identified by the company to 7.

The company also provided a narrative of their exclusion rationale in Section 7.3.2 of the submission. The reasons provided for exclusion were clear and were consistent with the scope. The company excluded 2 papers that were technically in scope on the basis they presented preliminary data that was reported elsewhere in later papers. The excluded papers were the early description of the BREATHE study Stankiewicz *et al.* (2009 and 2010) [11, 45]. The EAC agrees that it was appropriate to exclude these studies.

The company used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology to report on the studies identified [46]. This was clearly presented in Figure B7.1 of the submission.

3.3 *Included and excluded studies*

3.3.1 Company's included and excluded studies

The studies included by the company are listed in Table B7.2 (published studies) and Table B7.3 (unpublished studies) of the submission. In total, the company identified 11 published papers and 2 papers derived from unpublished sources. A summary of these studies, with interpretation of suitability for inclusion, is provided in Table 3.1. On occasion, a single study has been reported at different follow-up points. As such, there were less primary studies than reported papers. There were 9 unique studies described in total (7 published and 2 unpublished). Additionally, 1 of the papers provided a meta-analysis of several studies.

The key study identified was an RCT which has been given the acronym the REMODEL trial (Randomized Evaluation of Maxillary antrostomy versus Ostial Dilation Efficacy through Long-term follow-up). This study was described in 3 peer-reviewed papers: Cutler *et al.* (2013) [2], Bikhazi *et al.* (2014) [3], and Chandra *et al.* (2016) [4]. The REMODEL study compared XprESS or FinESS balloon dilation with FESS in adult patients with maxillary sinus disease with or without anterior ethmoid disease. This was the only experimental comparative study reported involving the XprESS system.

All the other studies identified were single-armed observational studies that reported the use of XprESS or FinESS balloon dilation in various populations of patients suffering from CRS or related sinus disease. Chronologically, the first published observational study was named the BREATHE (Balloon REmodeling Antrostomy THErapy) study, and was reported in 3 sequential papers: Stankiewicz *et al.* (2011) [47], Cutler *et al.* (2011) [10], and Stankiewicz *et al.* (2012) [12]. The RELIEF (HealthcaRE UtiLization and outcomes of FInESS Treatment on the Office) study was reported in 2013 by Levine *et al.* [9]. The study by Eloy *et al.* (2012) [14] was the only retrospective study included by the company. The XprESS Maxillary Pilot Study by Gould *et al.* (2012) [8] was published as a white paper and was not peer reviewed. The XprESS registry by Brodner *et al.* (2013) [7] and XprESS multi-sinus study by Gould *et al.* (2014) [6] were both prospective observational studies.

3.3.2 EAC's included and excluded studies

The EAC undertook an additional literature search (Section 3.1) which returned a total of 1,204 records. These were deduplicated both within the set and against the EAC re-run of the company's literature search, leaving 545 records. 128 of these were excluded as irrelevant using title searches in Endnote, leaving 417 records for manual review of title and abstract. This has

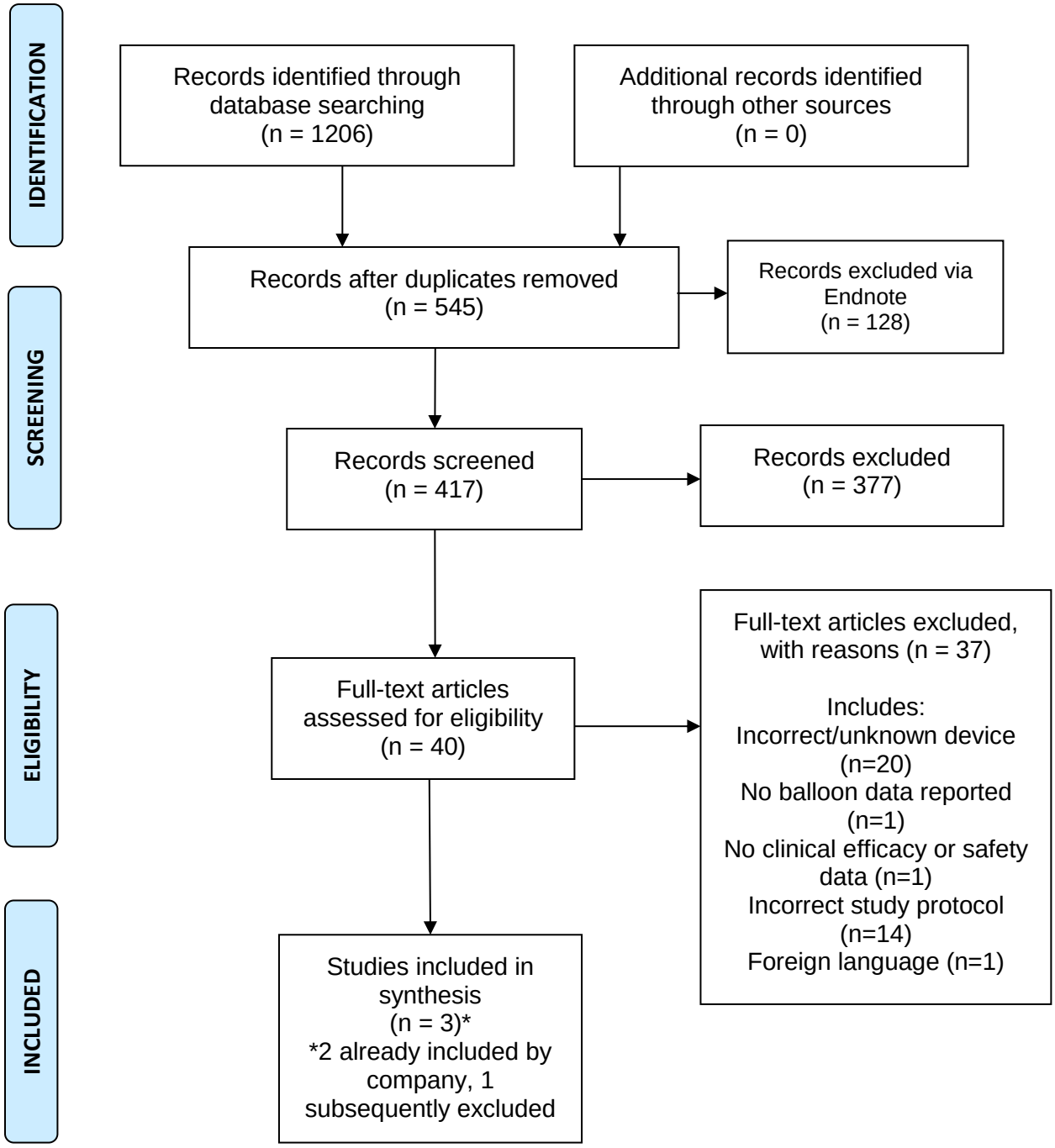
been illustrated as a PRISMA diagram in Figure 3.2, which reports results from the EAC's additional search only. After exclusion of papers that were obviously not relevant to the decision problem through inspection of the title and/or abstract alone, 40 full papers were retrieved for full consideration. Of these 40, 37 were excluded for the reasons given below:

- No reported data on Entellus balloon devices, or balloon devices not stated.
- No reported data on balloon devices.
- No clinical efficacy or safety data. The EAC also excluded case reports on this basis; although these were considered for safety data (see Section 3.7).
- Study protocol. Ongoing studies are discussed in Section 2.2.
- Foreign language.

This left 3 studies which were considered by the EAC for inclusion in this report (in addition to those studies identified in the re-run of the company's search in Section 3.3.1). Two of these studies had had already been identified by the company. These were the studies by Chandra *et al.* (2016) [4], which the EAC identified in its own literature search but not in its rerun of the company's search, and the white paper study by Gould *et al.* (2012) [8], which the company had identified through sources other than database searching, but was identified by the EAC in its search.

The final study identified by the EAC was the study by Brodner *et al.* (2013) [33]. This was a retrospective observational study that stratified patients with RARS or CRS according to the degree of septal deviation they exhibited. This study was subsequently excluded by the EAC after it was confirmed with the company that it was derived from patients investigated in several other studies sponsored by Entellus Medical including BREATHE, XprESS Maxillary Pilot, and XprESS Multisinus studies (correspondence log, page 22).

Figure 3.2: PRISMA flow diagram showing studies assessed from the EAC's additional literature search



Studies excluded by EAC

The EAC considered that 1 study that was included by the company should be excluded on the basis of the population it reported on. This was the study by Eloy *et al.* (2012) [14]. This was a small retrospective case series (n = 5) which investigated the use of standalone XprESS balloon dilation in patients who had previously undergone a failed frontal sinustomy. Revision surgery was not listed in the population or subgroup domains of the scope.

Studies considered by EAC to be of limited usefulness

The EAC considered the 2 unpublished studies identified by the company were technically within the scope, but were of limited value to the decision problem:

- The FinESS registry study was published as a protocol on clinicaltrials.gov [13]. However, this study has not been subsequently published or peer reviewed in full, and was provided to the EAC in abstract form only. As it was not possible to appraise this study, and only limited outcomes were reported, the EAC has not considered this further. Data from the FinESS registry did contribute to the meta-analysis by Chandra *et al.* (2016) [4].

- The Sinus Balloon Dilation in Paediatric Patients study by Soler *et al.* (2016) is expected to be published in 2016, and has been registered as a protocol on clinicatrials.gov [29]. This was a single-armed prospective observational study (n = 50) that was provided to the EAC as an abstract that did not allow for critical appraisal, and only limited results were reported. This was the only study that was reported in children. Although children were technically in the scope of the decision problem (as a subgroup), the EAC understands through clinical experts that sinus surgery is rarely performed in this age group in England (Section 2.3). For these reasons, this study has not been considered further by the EAC.

These studies are therefore included for completeness but the results do not contribute to this assessment report.

Studies considered by the EAC to be of borderline relevance for inclusion

The EAC considered that the study by Brodner *et al.* (XprESS registry, published in 2013) [7] could be interpreted as being out of scope, as the majority of patients enrolled received hybrid surgery, and these could not be disaggregated from patients receiving standalone treatment. However, this

study was retained as it specifically used the XprESS MSDS as the balloon intervention and provided data on treatment of multiple sinuses (including patency). The EAC has summarised the key details of all the included studies in Table 3.1.

Table 3.1: Key details of the studies included by the company and the EAC

Publication (Study)	Population Sinuses affected	Follow-up timeframe (sample size)	Intervention (I) and comparator (C)	Outcomes	Summary Usefulness* EAC comment
Cutler *et al.* (2013) [2] REMODEL	Adult patients with CRS or RARS Maxillary and/or anterior ethmoid sinuses.	Baseline (92) 6 months (n91)	I: Standalone XprESS or FinESS balloon dilation Data not disaggregated but reported by company to be proportionately equal. C: FESS	Changes in SNOT-20 (primary) Debridement frequency Technical success Nasal bleeding Recovery time Analgesic use Ostia patency Activity impairment, work impairment, productivity loss Patient satisfaction Revision rate Safety (adverse events)	**KEY STUDY** REMODEL RCT was the only comparative study and is therefore considered the key source of evidence. Patient recruitment was increased in the paper by Chandra *et al.* (2016) meaning results from individual published papers differ. This paper also reported a meta-analysis (see Section 3.8).
Bikhazi *et al.* (2014) [3] REMODEL		12 months (89)			
Chandra *et al.* (2016) [4] REMODEL		Baseline (133) 6 months (133) 12 months (119) 18 months (66) 24 months (15)			
Gould *et al.* (2014) [6] XprESS multi-sinus study	Adult patients with CRS or RARS All patients had maxillary sinus disease as minimum. Some patients with frontal, sphenoid, and/or ethmoid disease.	12 months (82)	I: Standalone XprESS balloon dilation C: None (baseline)	Changes in SNOT-20 (primary) Rhinosinusitis symptom inventory (RSI) score Medication use Productivity/reinfection Revision rate Subject satisfaction Safety (adverse events)	**USEFUL STUDY** This was the only study that investigated the use of standalone XprESS MSDS in multiple sinuses (including the frontal and sphenoid sinuses)
Brodner *et al.*	Adult patients with	Baseline (175)	I: Standalone	Changes in SNOT-20	**VERY LIMITED USE**

Publication (Study)	Population Sinuses affected	Follow-up timeframe (sample size)	Intervention (I) and comparator (C)	Outcomes	Summary Usefulness* EAC comment
(2013) [7] XprESS registry	CRS Primarily patients treated for frontal sinus disease. Smaller numbers of patients treated sphenoid and maxillary disease.	12 months (44)	XprESS balloon dilation Hybrid surgery using XprESS MSDS C: None (baseline)	(primary) Patency Medication use Work productivity Reinfection rate Revision rate Serious adverse effects	Not possible to disaggregate patients receiving standalone or hybrid treatment. Excluded from meta-analysis [4]
Gould *et al.* (2012) [8] XprESS Maxillary Pilot Study	Adult patients with CRS or RARS Maxillary sinus (all) Anterior ethmoid sinus (some)	6 months (21)	I: Standalone XprESS balloon dilation C: None (baseline)	Changes in SNOT-20 (primary) Technical success Medication use Recovery time Revision rate Serious adverse effects	**LIMITED USE** Small case series published in white paper (not peer reviewed)
Levine *et al.* (2013) [9] RELIEF study	Adult patients with CRS or RARS Maxillary and anterior ethmoid disease.	Baseline (69) 12 months (64)	I: Standalone FinESS balloon dilation C: None (baseline)	Changes in SNOT-20 (primary) Technical success Tolerance Debridements RSI Medication use Work productivity Reinfection rate Revision rate Serious adverse effects	**LIMITED USE** XprESS MSDS not used. Patients excluded if they had any other sinuses affected.
Cutler *et al.* (2011)	Adult patients with	Baseline (71)	I: Standalone	Changes in SNOT-20	**LIMITED USE**

Publication (Study)	Population Sinuses affected	Follow-up timeframe (sample size)	Intervention (I) and comparator (C)	Outcomes	Summary Usefulness* EAC comment
[10] BREATHE study	CRS Maxillary sinus	12 months (67)	FinESS balloon dilation C: None (baseline)	Technical success Recovery time Revision rate Work Limitation Questionnaire (WLQ) Work Productivity and Activity Impairment (WPAI) Subject satisfaction Serious adverse effects	Patients were excluded if they had disease of the frontal, posterior ethmoid, or sphenoid sinuses
Stankiewicz *et al.* (2012) [12] BREATHE study		27±3.6 months (59)			
FinESS registry (2011) [13]	Adults with CRS Maxillary and ethmoid sinuses	Baseline (155) 12 months (137)	I: Standalone FinESS balloon dilation C: None (baseline)	Change in SNOT-20 Technical success Work productivity Reinfection rate RSI score Revision rate Serious adverse effects	**VERY LIMITED USE** Unpublished abstract Data used in meta-analysis
Soler *et al.* (2016) [29]	Paediatric patients with CRS (2 to 21 years)	6 months (50)	I: Standalone XprESS balloon dilation C: None (baseline)	Change in SNOT-22 Technical success RSI Change in SN-5 (Sinus and Nasal Quality of Life Survey	**VERY LIMITED USE** Unpublished abstract Only evidence reported in children, unknown generalisability
* EAC's interpretation of usefulness to decision problem, based on study type, quality of study, and applicability to scope.					

3.3.3 Accounting for participants

The company accounted for the participants enrolled in the studies in Table B7.13 of the submission. The total number of unique patients studied overall was reported. As there was some ambiguity in the text of some of the studies on where and how the patients were enrolled, the EAC confirmed with the company that all patients in all studies and within the meta-analysis were unique (correspondence log, page 22).

3.4 *Overview of methodologies of all included studies*

The company provided 3 types of the study to support the claims of clinical effectiveness of the XprESS MSDS (or FinESS system).

- Firstly, the company reported on the REMODEL study [2]. This was an RCT that provided the only comparative data between balloon dilation and FESS. Whilst RCTs are considered to provide the highest level of primary evidence, the REMODEL trial did have some limitations (see Sections 3.5.2 and 3.5.3).

- Secondly, the company reported on several single-armed observational studies [6-10, 12] that provided supportive longitudinal data relevant to the decision problem (Section 3.5.5).

- Thirdly, the company reported a meta-analysis that pooled patient data from both the observational studies and the REMODEL trial [4]. This provided a useful summary of the available evidence on Entellus balloon dilation. This is discussed in Section 3.8.

The company comprehensively and accurately described the methodology of each study in Tables B7.4 to B7.12 of the submission. The EAC considered that the use of paired and unpaired statistical analysis was appropriate throughout the included studies.

3.5 *Overview and critique of the company's critical appraisal*

The EAC has critically appraised the included studies, with particular attention given to the REMODEL RCT.

3.5.1 Company critical appraisal of REMODEL study

The company provided a critical appraisal of the REMODEL trial using the recommended critical appraisal tool for RCTs supplied by NICE. This is reported in Table B7.14 of the company's submission; a supporting narrative was not supplied. The EAC has reviewed this appraisal and agrees with its content in terms of response and how this was evidenced (how the questions were addressed by the study). Whilst generally agreeing with the company's appraisal (with the exception of how dropouts were accounted for, see Section 3.5.2), the EAC considered that because this study was so pivotal to the company's submission, a more detailed appraisal was useful. The EAC has provided a narrative of this in the following sections, which critically appraises in detail the internal validity (i.e. the methodological quality of the study itself) and external validity (i.e. how it specifically applies to the decision problem) of the REMODEL trial.

3.5.2 EAC critical appraisal of internal validity of REMODEL study

Study design

The REMODEL study was a prospective, multi-centre, non-inferiority, parallel RCT; the methodology of which was comprehensively reported in the paper by Cutler *et al.* (2013) [2]. This type of trial design is regarded as the highest quality of primary evidence for the assessment of medical interventions [48] and was an appropriate choice. The trial compared the use of FESS (that consisted of maxillary antrostomy and uncinectomy, with or without anterior ethmoidectomy) with balloon dilation systems manufactured by Entellus Medical in adult patients with CRS or RARS. The EAC understands through the company that the systems used were the XprESS MSDS and the FinESS system in a ratio of approximately 50:50 in the intervention arm, although this was not reported in the study (correspondence log, page 7). It has been assumed that these systems are functionally equivalent (see Section 2.3.2). The nature of patients enrolled into the trial is essential in understanding the applicability of the study to NHS practice (see Section 2.3.1).

Although the EAC agrees that the trial adequately addressed the effectiveness of balloon dilation relative to FESS in the patients selected, the trial did not attempt to measure the absolute effects of either intervention by including a control arm of patients who continue receiving maximal medical treatment but no surgery (or sham surgery), thus the natural history of the

condition cannot be elucidated. However, the EAC accepts that a lack of clinical equipoise would make this unethical (see Section 2.1.2).

Randomisation and Blinding

The study described the enrolment of patients and the randomisation procedure, which was performed by an independent statistician. This procedure was described in more detail in Table B7.4 of the company's submission than in the published paper. Patients and clinicians were blinded to their allocation (delivered through sealed envelopes), and concealment of allocation was maintained. This meant that the potential for selection bias was greatly reduced. This is supported by the fact there was no statistically significant differences in demographics or other characteristics between the 2 patient groups at baseline.

Following randomisation, the study reported that it was not feasible to blind the patients or treating physicians to the treatment allocation because procedurally they were very different (including the setting undertaken, use of anaesthesia etc.). However some post-surgical assessments were performed or audited by independent physicians, such as requirement for debridement, and the statistical analysis was performed blinded. Whilst the EAC accepts that it was not practicable to improve on the blinding used in the study, it should be considered that the lack of blinding might potentially lead to expectation and performance bias, particularly as the primary outcome was prone to subjectivity [49].

Sample size, power calculation and statistical analysis

The primary effectiveness outcome of the trial was changes in symptom improvement as measured by SNOT-20, with a reduction of 0.8 (inferiority margin) being considered to be clinically important in a previous psychometric study [50]. The authors of the trial opted to use a non-inferiority design; this is appropriate if the primary aim of the study is to address concerns that the new intervention is not inferior to the older intervention by the specified margin. Once "non-inferiority" has been satisfied, other advantages of the new treatment may be explored, such as reduction in the need for post-surgical care.

Using a one-sided alpha-level of 0.025, it was calculated that 36 patients would be required in each arm, and this was surpassed during recruitment. The EAC was satisfied this calculation was correct; however, the rationale for adopting a non-inferiority design should have been more clearly explained in the narrative [51].

Patient withdrawal and attrition

The REMODEL study initially enrolled 52 patients in the balloon arm and 53 in the FESS arm. However, following randomisation, 11 patients withdrew from the FESS arm compared with only 2 in the balloon arm. Of these patients, 8 in the FESS arm withdrew because they did not want FESS, compared with only 1 patient who was unhappy with the prospect of treatment with balloon dilation, which led to uneven treatment groups (50 in balloon arm compared with 42 in the FESS arm). In the longer-term follow-up study by Chanda *et al.* (2016) [4] the attrition rate was not published, but the EAC established from the company that only 3 patients in the FESS arm withdrew following randomisation, which was consistent with the initial cohort (correspondence log, page 23). A *post hoc* modified intention-to-treat (ITT) analysis was conducted, whereby patients who refused or otherwise did not receive surgery after randomisation were excluded from analysis. This approach to analysis has been associated with bias [52]. The EAC understands from the company that results from an informal *post hoc* analysis consisting of imputation from the last observation carried forward insignificantly favoured XprESS MSDS; however, the EAC maintains the lack of published full ITT analysis remains a limitation of the study.

If the patients who dropped out pre-surgery differed from the remaining population (for instance, they had less severe CRS) then the higher withdrawal from the FESS arm may have introduced attrition bias, in which the groups of patients being compared no longer have similar characteristics. Ideally, the authors of the study should have followed up the withdrawn patients so that full ITT could have been additionally performed. Instead, the results of modified ITT analysis may be considered to provide a lower level of evidence. Trials employing analysis per protocol have been observed to exhibit larger effect sizes than those using ITT analysis [53].

Patient drop out and loss to follow-up following surgery was low. Two papers reported longer-term outcomes. Eighty nine of the original patients (96.7%) were successfully followed up at 1 year as reported in the paper by Bikhazi *et al.* (2014) [3]. However, only 25 patients (27%) of the original cohort had 24 month follow-up data at the time of publication of Chandra *et al.* (2016) [4]. There are 2 consequences of this. Firstly these 25 patients may not represent the treatments and outcomes for the entire cohorts (e.g. received proportionately more FinESS than XprESS intervention). Secondly, the low sample size reduces overall confidence in the results.

Outcomes and statistics

In addition to the primary outcome of symptom improvement, the authors also reported a “primary” endpoint to show balloon superiority over FESS for post-operative debridement rate. The power calculation to support the required sample size of 23 patients per arm was not pre-specified in www.clinicaltrials.gov, and there was insufficient information reported (for instance what a clinically important difference in debridement rate is) to repeat the analysis. The EAC notes that this outcome, as well as all the secondary outcomes reported, were not published on the trial protocol on clinicaltrials.gov [5]. This causes the potential for reporting bias. However, the EAC was satisfied that the statistical reporting of results was appropriate, and the use of the Benjamin-Hochberg adjustment for multiple comparisons should have reduced the potential for reporting bias [54].

The results reported several subgroup analyses as longitudinal changes (compared with baseline) or comparisons of interventions. The EAC considered a subgroup analysis by presence or absence of nasal polyps would have been informative. In addition, no outcome concerning nasal polyps were reported (such as number, size, polyp severity).

3.5.3 EAC critical appraisal of external validity of REMODEL study

The EAC flagged several issues concerning the design and reporting of the REMODEL study and its generalisability to the decision problem. The following section summarises these issues according to a patient, intervention, comparator, outcome (PICO) analysis.

Population

The patients recruited into the REMODEL trial were relatively highly selected and may differ to patients presenting to secondary care in the England (see Section 2.3.1), particularly concerning the sinus affected, disease severity and complexity, stage in disease process, and the presence or absence of nasal polyps:

- Disease complexity. The REMODEL trial was conducted in people with uncomplicated CRS or RARS, affecting only the maxillary with or without anterior ethmoid sinuses. Patients with disease of the frontal or sphenoid sinus, gross sinonasal polyposis or who had previously undergone sinus surgery[1] were excluded. Therefore the comparative efficacy of balloon dilation in these patients is not answered by this study.

- Stage in disease process. As described in Section 2.1.2, surgical management of CRS and RARS is typically considered after medical management options have been exhausted. This may entail several months' use of ICS as well as intermittent use of oral corticosteroids and antibiotics. Although patients included in the REMODEL study were described as refractory to medical treatment and inclusion criteria were clearly described according to healthcare insurance criteria, it is unclear whether the maximal use of medication was equivalent to that used typically in the NHS. Issues such as earlier access to surgical treatment may also mean that trial patients were less maximally treated than those in the NHS.

- Nasal polyps. The presence or absence of nasal polyps is an important aspect of the classification of CRS and determinant of treatment according to EPOS guidelines [21], with patients with nasal polyposis typically receiving more aggressive surgical management and benefitting more from this. The REMODEL trial excluded patients with gross polyposis but otherwise did not report subgroup analysis on whether there were differences in response to treatment in patients with mild to moderate polyposis.

Table 3.2 compares the baseline characteristics of patients included within REMODEL to those included within the national audit [2, 37]. Although the national audit reports on data from 2000, EAC experts advised that much of the data will still be relevant (correspondence log, appendix 1, collated responses, page 2).

[1] Note 16% of included patients had had nasal surgery, however.

Table 3.2: Comparison of baseline characteristics of patients in REMODEL trial (2013) and National Audit

	National Audit all patients [15]	National Audit sinus only (no polyp removal) [15]	REMODEL balloon arm [10]	REMODEL FESS arm [10]
Mean age, years (range)	49.5 (16-94)	43.9 (16-81)	47 (+/- 14.6)	47 (+/- 14.5)
Male	60%	45%	32%	45%
Non or former smoker	80%	75%	86%	88%
Current smoker	20%	25%	14%	12%
Asthma/bronchitis	33%	21%	16%	19%
Previous nasal surgery	46%	35%	14%	19%
Baseline Lund-Mackay score	10.6 (95%CI: 13.2-14)	7.0 (95%CI: 6.7-7.3)	3.2 (±3.2)	3.6 (±3.5)
Duration of disease	54% had symptoms for more than 5 years	50% had symptoms for more than 5 years	12.4 (+/-13.0) years	12.7 (+/-13.9) years
Baseline SNOT score*	Total SNOT-22: 42 (95% CI 41.2-42.7)	Total SNOT-22: 43.7 (95% CI 42.4-45.0)	Average SNOT-20: 2.54 (±0.91)	Average SNOT-20: 2.54 (±0.79)
* Note that the baseline SNOT scores differ between the audit and REMODEL trial in two ways and are therefore not directly comparable. The audit used an absolute *total* SNOT-22 score, whilst the REMODEL trial used a *mean average* of the SNOT-20 score.				

The REMODEL study included a smaller proportion of smokers, a smaller proportion of people with asthma or bronchitis and a smaller proportion of people who had had previous nasal surgery[1] than the national audit.

The baseline Lund-Mackay scores of included patients, within the REMODEL study were substantially lower than those included within the national audit, whereby a higher score represents a high severity of disease. Experts advised that the decision to perform surgery on a patient is not based on Lund-Mackay scores, but rather clinical symptoms (correspondence log, appendix 1, collated responses, page 15). However, they added that a score of 4.26 (higher than both arms of the REMODEL study) is normal for an adult.

The duration of disease was not comparable between the 2 studies given that the data were provided in different formats.

Likewise, the baseline SNOT scores were difficult to compare given that the national audit used the total SNOT-22 measure whilst the REMODEL study used the average SNOT-20 measure. In both measures scores for each question are ranked on a scale of 0-5 where 5 represent greater severity of problem [55, 56]. Advice from a clinical expert specified that the mean SNOT-22 score cannot be determined simply by dividing the total score by the number of questions. He further stated that one would require the symptom specific scores from both datasets in order to make a comparison. However, the EAC do not have access to this data.

The EAC posed an additional question to the clinical experts to clarify the clinical significance of difference in baseline characteristics between the group of patients in REMODEL and those in the national audit. Three experts responded (see correspondence log, page 31). The first advised that the low Lund-Mackay score reported in the baseline population of the REMODEL trial indicated the patients had isolated maxillary sinus disease and that these patients would make up a small subgroup of those being operated on within the NHS.

The second expert advised that the patients within REMODEL would be a reasonable subgroup of those treated within the NHS, with limitations. Given that the REMODEL study is limited to maxillary sinus disease with some anterior ethmoid surgery in some patients the Lund-Mackay scores would be expected to be low. Furthermore, the national audit included a small proportion of patients with recurrent acute sinusitis, but most patients had CRS with bilateral change and more extensive sinus change, hence higher Lund-Mackay scores.

The third expert had concerns that those in the REMODEL trial comprise a different patient population than those included within the national audit. Furthermore, he advised that as a rule of thumb he doesn't typically operate on patients with SNOT-22 scores of less than 10 and Lund-Mackay scores of less than 4. However, patients may have low Lund-Mackay score if they have a blocked maxillary sinus on one side only (see correspondence log, appendix 1, collated responses, page 15).

On balance, the EAC concludes that the population enrolled in the REMODEL trial is likely to comprise a subgroup of the full spectrum of patients treated in the NHS and not fully representative [4]. This uncertainty has been reflected in the conclusions drawn by the EAC.

Intervention

The intervention arm used in the REMODEL trial was restricted to balloon dilation only, which is a strength of the study as it enabled isolation of the effect of the balloons from other surgical methods. However, in practice hybrid techniques whereby FESS and balloon dilation are combined may be undertaken, for instance where there is extensive soft tissue disease and/or nasal polyposis. Additionally, around half the patients in the REMODEL trial received the predecessor technology FinESS rather than the XprESS MSDS. The EAC has assumed there is clinical equivalence between these interventions, but notes this has not been demonstrated in head-to-head studies (see Section 2.3.2).

Outcomes

The primary outcome of the REMODEL trial, SNOT-20 score, was considered relevant to the NHS, being a validated measure of symptom improvement and relevant to patient benefit [36]. However, the other "primary" outcome of frequency of debridements might not be generalisable to current management in England because routine post-surgical debridements are not routinely performed in the NHS (see Section 2.1.2). It should be noted that follow-up was reported at 24 months in a limited cohort of patients [4]; however, results were extrapolated up to 5 years in the *de novo* economic model (see Section 4.2).

3.5.4 EAC critical appraisal of published observational studies

The EAC has critically appraised the REMODEL study [2] and its updates [3, 4] and has summarised the strengths and weaknesses of the study in Table 3.3. The REMODEL study was a prospective RCT directly relevant to the decision problem. The study was of sound methodological quality and but lacked internal validity due to loss of randomisation. Specific strengths of the study included its clear reporting of patient selection, randomisation procedures (pre drop-outs), blinding where feasible, and reporting of outcomes. However, a key limitation of the trial was the high attrition immediately following randomisation and the use of a subjective primary outcome when blinding was not feasible. Other weaknesses pertain more to the generalisability of the evidence to the NHS setting than the study protocol *per se*.

An inevitable consequence of adopting a tightly controlled experimental approach to the study, whereby the effect of the intervention is isolated and restricted to selected patients, is the need for assumption or extrapolations to be made when applying the evidence to broader patient groups.

Table 3.3: Summary of the strengths and weaknesses of the REMODEL trial incorporating internal and external validity

	Strengths	Weaknesses
Study design	Parallel RCT, strongest form of primary evidence providing comparative outcomes with current standard practice.	Non-inferiority design can only show intervention is not substantially "worse" than comparator. Rationale for non-inferiority not clear. Absence of "do nothing" arm means absolute effect of either arm not known.
Patient selection	Well described inclusion and exclusion criteria. Appears to reflect eligible population for treatment according to US insurance company criteria.	Might not reflect population indicated for FESS in the UK (e.g. regarding maximal medical treatment). Selection limited to uncomplicated maxillary sinus disease with or without anterior ethmoid disease. Presence and absence of mild to moderate nasal polyps not clearly documented. *Risk of spectrum bias.*
Randomisation	Randomisation performed with adequate concealment of allocation. *Low risk of selection bias*.	Randomisation lost due to drop-outs in FESS arm post randomisation.
Blinding	Independent and blinded audit controls. Blinded statistical assessment.	Not feasible to blind patients or treating/assessing clinicians. Subjective primary outcome. *Moderate to high risk of performance bias*.
Patient attrition	Reasons for patient withdrawal documented. Withdrawal low following surgery and evenly spread between arms. *Modified ITT* analysis appropriate (but weaker evidence).	High withdrawal from FESS group prior to surgery led to uneven groups. Low number of eligible patients reporting data at 24 months, so poor confidence in longer term results and risk of bias in results (e.g. disproportionate use of FinESS system).

		High risk of attrition bias.
Reporting of outcomes	Primary analysis pre-specified in protocol. SNOT-20 directly related to patient benefit. Extensive reporting of secondary outcomes with appropriate control for multiple comparisons.	Second "primary outcome", frequency of nasal debridement may not generalise to NHS care and was not pre-specified in research protocol. Outcomes limited to 24 months (in a small cohort of patients only). SNOT-20 is subjective primary outcome and could be influenced by participants' perceptions.
Statistical analysis	Power calculation for sample size for primary outcome performed. Correction for multiple comparisons performed. *Low potential for reporting bias.*	Sample size requirement for nasal debridement not clear.
Study company	Three lead investigators declared no conflict of interest	Study was funded by Entellus Medical. Two lead investigators paid consultants of Entellus Medical.

3.5.5 Summary of quality and applicability of observational studies

The company identified 4 observational studies from the literature that investigated the use of XprESS or FinESS balloon dilation in the relevant patient population to the scope (with the EAC having excluded the study by Eloy *et al.* (2012) [14] as being out of scope). The company accurately described the methodology of these studies in Section 7.4.1 (Tables B7.5, B7.6, B7.7, B7.9, and B7.10). The company critically appraised each of these studies in Section 7.5 using the recommended template for observational studies (Tables B7.15, B7.16, B7.17, B7.19, and B7.20), but did not provide a narrative summary of the quality of these studies.

The EAC noted that all of the observational studies identified were prospective single-armed studies and therefore provided only longitudinal data (sometimes described as "before and after" data). A fundamental limitation of this study type is that they do not provide comparative data with which an assessment of the relative efficacy of different interventions can be made. Prospective case series also typically cannot control for sources of bias or for confounding factors, whether known or not. For these reasons, results generated from the observational studies reported in the submission should be treated with caution. However, these studies do provide useful supportive evidence to the REMODEL trial.

A brief narrative of the methodological quality of each observational study, drawing attention to any strengths and weaknesses, is provided by the EAC in the following sections.

XprESS Multi-Sinus Study

This was a single-armed prospective observational study authored by Gould *et al.* and published in 2012 [6], and was critically appraised by the company in Table B7.15; the EAC agrees with the content of this appraisal.

This study prospectively enrolled 82 adults with CRS or ARS, although the method of recruitment (consecutive or otherwise selected) was not reported. The primary outcome was the measurement of change of sinonasal symptoms 1 year after receiving XprESS MSDS in an office environment (using SNOT-20). To be eligible for treatment, patients had to have maxillary sinus disease as a minimum although patients with additionally affected sinuses (frontal, sphenoid, ethmoid) were also included. Other reported outcomes included patient satisfaction with treatment, frequency of severe adverse effects, and the rate of revision surgery. Analysis was performed using baseline characteristics as the control. Additionally, subgroup analysis was also performed according to the sinuses affected.

The main strengths of this study was that it was specific to the XprESS MSDS technology and included patients with different and multiple sinuses affected, who were subject to subgroup analysis. The baseline characteristics of patients were well documented and appeared to represent the population of interest (patients with refractory CRS or RARS). Therefore the study was reasonably generalisable to NHS practice (with caveats, see Section 2.3). Additionally, the cohort enrolled was relatively large (n = 82) and the follow-up rate after 1 year was good, with 94% of enrolled patients providing data. One specific weakness of the study, however, was the lack of description of how the patients were enrolled, lending the possibility of selection bias.

XprESS Registry

The XprESS registry, published in 2013 by Brodner *et al.* [7], was the first full clinical study of the XprESS MSDS. This was a single-armed observational study that was focussed on safety as the primary outcome, although effectiveness outcomes were also pre-specified [30]. It was critically appraised by the company in Table B7.16. Patients (n = 175) were enrolled if they required treatment of the frontal recess and sphenoid sinus ostium and/or maxillary ostium or ethmoid infundibulum and had been previously scheduled for treatment with FESS. Outcomes at 1 month (for all patients) included device safety, technical success, and procedural outcomes. Additionally, the first 50 patients were followed to 1 year for outcomes of safety, QoL as measured by the SNOT-20 and RSI, revision rate, and ostial patency.

The EAC considered the strengths of this study were that it was specific to the XprESS MSDS and patients were recruited according to FESS criteria. This was a relatively large study, with 175 patients enrolled (and 497 balloon dilations performed). However, there were limitations to the study's generalisability in that hybrid surgery was extensively performed in this study and results could not be disaggregated across the components. In consequence it was not possible to isolate the effect of balloon dilation alone.

The XprESS Maxillary Pilot Study

The XprESS Maxillary Pilot Study by Gould *et al.* was published in 2012 as a white paper (not peer reviewed) [8]. This was a single-armed prospective observational study critically appraised in Table B7.17 of the company's submission. Adult patients with uncomplicated refractory CRS or RARS of the maxillary or anterior ethmoid sinuses were enrolled (n = 21). Although patient demographics were described the recruitment strategy was not. All patients received XprESS MSDS under local anaesthesia, and the main outcome was

change in SNOT-20 score from pre-procedure to up to 6 months post-procedure.

A relative strength of this study was that it only employed the technology of interest, the XprESS MSDS. However, only patients with maxillary or anterior ethmoid disease were included, and only 21 patients were studied, meaning generalisability and confidence in the results were low. Other weaknesses included the lack of reporting of secondary outcomes and absence of peer review, although the study protocol was published [57].

The RELIEF study

The RELIEF study by Levine *et al.* was published in 2013 [9] and critically appraised by the company in Table B7.19. This was a single-armed prospective observational study with a published protocol [58]. This study recruited adult patients with refractory CRS or RARS affecting the maxillary and anterior ethmoid sinuses. The primary outcome of this study was QoL as measured by SNOT-20 and RSI. Other outcomes measured included technical success, revision rate, and safety.

This was a medium sized study recruiting 74 patients with follow-up at 1 year. The generalisability of this study with relation to the decision problem was limited in that it investigated the use FinESS system with no patients receiving XprESS MSDS (although the EAC has assumed equivalence of these technologies this is an area of uncertainty, see Section 2.3.2). Consequently, enrolment was restricted to patients with maxillary with or without ethmoid disease.

The BREATHE study

This study was published in 3 papers: Stankiewicz [11, 12] (2010 and 2012) and Cutler [10] (2011). This study was critically appraised by the company in Table B7.20. This was the first published study of an Entellus balloon product and was exclusively performed using the FinESS system in patients with CRS of the maxillary and/or ethmoid sinus. As with the other studies described, this was a single-armed prospective study, and 71 patients were recruited. Follow-up was up to 2 years with the primary outcome of QoL improvement measured using SNOT-20, ostial patency at 3 months, and device related safety. Follow up was up to 2 years post procedure. An additional paper reported Work Productivity and Activity Impairment (WPAI) Questionnaire and Work Limitation Questionnaire (WLQ) at 1 year follow up [47].

The BREATHE study had limited application to the decision problem because it used the older predecessor FinESS technology. This system requires a

more invasive trans-antral approach and can only be used to treat the maxillary ostia or the ethmoid infundibulum (see Section 2.3.2).

Summary of quality and applicability of observational studies

The EAC's assessment of the strengths and weaknesses of the observational studies are summarised in Table 3.4.

Table 3.4: EAC's summary of critical appraisal of observational studies

	Methodological quality*	Reporting quality**	Applicability to decision problem***	EAC comment
XprESS Multi-sinus study [6]	Good	Good	High	Only study that reported outcome data on all sinuses.
XprESS registry [7]	Good	Good	Low	Largest single study reported on an Entellus balloon system. Allowed extensive use of hybrid treatment.
XprESS Maxillary Pilot Study [8]	Poor	Poor	Medium	Small study. Not peer reviewed.
RELIEF study [9]	Good	Good	Medium	FinESS system only.
BREATHE study [10, 12, 47]	Good	Good	Medium	FinESS system only.

* Methodological quality relative to studies of this type. All single armed observational studies are subject to extensive sources of bias and confounding.
** Reporting quality refers to how comprehensive the studies were described (e.g. whether the detail would allow the study to be repeated).
*** Applicability concerns how the population recruited and intervention used relate to the decision problem.

3.6 *Results*

The company summarised the results of the REMODEL trial in Table B7.23 and the results of the observational studies in Tables B7.24 to B7.31. The EAC has not repeated this work to avoid unnecessary duplication and document redundancy. The EAC has however, validated the results of these studies and assessed their relevance to the decision problem by:

- Cross referencing all the reported results in the company's tables with the original published papers (Section 3.6.1).
- Describing the key results of the REMODEL trial (the only comparative study) and assessing the degree of uncertainty in key results (Section 3.6.2).
- Describing the key results from the observational studies (Section 3.6.3, and Section 3.8).
- Addressing how the evidence presented supports the outcomes of the XprESS MSDS described in the decision problem and claimed benefits (Section 3.6.4).
- Assessed the company's interpretation of the clinical evidence (Section 3.6.5).

3.6.1 Cross reference of results

The EAC has cross-referenced the company's tabulated results with each other and the original published data. The EAC identified several discrepancies between the tabular data in the submission and the published data in the original papers, particularly concerning the REMODEL study. The most probable reason for these discrepancies was the way in which the REMODEL trial was conducted and reported. The first 2 publications, those of Cutler *et al.* (2013) and Bikhazi *et al.* (2104) [3], reported on a cohort of 92 patients who had received FESS or balloon dilation and results reported from these studies are used in this report. However, the follow-up paper by Chandra *et al.* (2016) [4] not only reported longer-term outcomes from the original cohort (at 18 and 24 months), but also an additional cohort of patients who had been subsequently randomised, so there was a total of 135 patients included in total for the early outcomes. Issues with the randomisation procedure and details of patient attrition in this later cohort were not reported, which is a weakness. Although this data was not reported in full in the later paper, it is likely that Entellus Medical were privy to the final trial data, which would explain the (usually small) discrepancies observed.

Given most of the errors were not material, for purposes of clarity and brevity, the EAC has not reported on the full list of discrepancies or omissions in this report. Instead, the EAC has reported data from published sources where available, and has only specifically reported on differences where the exact results might impact on the clinical and economic interpretation.

3.6.2 Results of REMODEL trial

Primary outcome (SNOT-20)

The primary outcome in the REMODEL trial was the mean change in SNOT-20 score between baseline and 6 months (for a description of the SNOT-20 score and how it is calculated see Section 2.3.4) [2]. This outcome was also measured in the short term at 1 week and 1 month and at in the longer term at 12 months [3], 18 months [4] and 24 months [4]. These results are summarised in Table 3.5.

Table 3.5: Changes in SNOT-20 score in patients treated with FESS or Entellus balloon dilation

Time period	XprESS ± SD (number of patients*)	FESS ± SD (number of patients)
Baseline (pre-procedure)**	2.54±0.91 (50)	2.54±0.79 (42)
1 week***	-1.49±0.87 (48)	-0.96±1.12 (41)
1 month	-1.70±0.98 (49)	-1.62±0.95 (40)
6 months (primary outcome of REMODEL)	-1.67±1.10 (49)	-1.60±0.96 (42)
12 months	-1.64±1.06 (48)	-1.65±0.94 (41)
18 months	N/A (37)	N/A (29)
24 months	-1.65 (15)	-1.45 (10)

* There were discrepancies of number of patients at some time points in different published papers.
** Baseline data presented as mean SNOT-20 score (absolute value)
*** Statistically significant difference between XprESS and FESS arms (p = 0.014).
N/A No numerical data available. Only graphical data was presented at 18 months.

The improvement in mean SNOT-20 scores compared with baseline was statistically significant in both groups at all time points ($p<0.0001$). Furthermore, in all cases this difference exceeded 0.8 and therefore was clinically meaningful. There was no statistical difference between XprESS balloon dilation and FESS at any time point, with the exception of 1 week where there was a significantly greater, but not clinically important, reduction in the XprESS MSDS arm. The results indicated non-inferiority (margin level 0.8) of balloon dilation compared with FESS.

The authors also reported subgroup and subscale analysis of the SNOT-20 score. At the primary endpoint of 6 months, it was found there was similar clinically significant improvements in all subgroups analysed (sinus type operated; presence or absence of accessory ostia or septal deviation; CRS or RARS) [2]. There was also significant improvement seen in each of the subscales of the SNOT-20 score (rhinological symptoms; ear and facial symptoms; sleep function; psychological issues). Furthermore, using the standardised effect size (see Section 2.3.4), the improvement in these subscales after 12 months was “large”.

In summary, the primary outcome of the REMODEL trial reported the following results:

- Balloon dilation (XprESS and FinESS) and FESS were associated with statistically significant and clinically important improvement in patient symptoms compared with baseline, as measured by SNOT-20.
- This effect was evident 1 week after treatment in both arms, where there was an immediate, clinically significant improvement which was maintained, plateauing out at 6 months and lasting for at least 24 months.
- Subgroup and subscale analysis showed that all patients benefitted in all the symptom domains.
- There was no statistical difference between balloon dilation compared with FESS in patient symptoms scores at any point in the 2 year follow-up with the exception of 1 week where there was a significantly greater, but not clinically important, reduction in the XprESS MSDS arm.

These results should be interpreted under the proviso that they apply to a selected population of people with CRS or RARS with maxillary with or without anterior ethmoid disease only. Longer term outcomes are based on low patient number (n = 10 in FESS arm). Additionally, the effects of treatment on patients with significant problems caused by nasal polyps are not known.

Secondary outcomes

The REMODEL trial included several secondary outcomes which are briefly discussed in the following sections.

Nasal debridement

The authors of the REMODEL trial listed nasal debridement as an additional primary outcome [2]; however the EAC considers that this was actually a secondary outcome as it was not pre-specified in the protocol [59] and power calculations appear to have been performed *post hoc*.

The authors reported that 92.0% (46/50) of patients in the balloon dilation arm did not require a postoperative debridement compared with 26.2% (11/42) of FESS patients. There was a mean of 0.1±0.6 (SD) postoperative debridement in the balloon arm compared with 1.2 ±1.0 in the FESS arm ($p < 0.0001$) [this was reported as 0.2 and 1.0 respectively in the submission]. The authors noted that the use of debridement may have been influenced by prior habits or beliefs of the surgeon, although there was no evidence of deviation from usual US practice in this study. The EAC understands from clinical experts that in England nasal debridement is not routinely performed following FESS (See Section 2.1.2).

Recovery outcomes

The authors reported no significant difference between balloon dilation and FESS in terms of post-discharge nausea and duration of over-the-counter pain (OTC) medication. The authors reported that FESS was associated with a statistically significant increased recovery time (return to normal activities, 1.6±11 vs 4.8±6.2 days, $p = 0.002$) and duration of prescription pain medication (0.9±1.4 vs 2.8±2.7 days, $p < 0.001$) compared with balloon dilation.

In the study, the authors also reported 14/50 (28.0%) patients in the balloon group were discharged with nasal bleeding, compared with 23/42 (54.8%) in the FESS group (p=0.009). Whilst a statistically significant difference in this outcome was also reported in the submission, the number were slightly different (32% versus 56%, p=0.009) based upon data in the most recent publication [4].

Rhinosinusitis episodes

Bikhazi *et al.* (2014) reported that patients in the balloon and FESS arms achieved significant reductions in rhinosinusitis episodes at 12 months following surgery compared with the year before (reductions of 4.2 and 3.5 episodes respectively, not significantly different) [3]. It is possible that these results might have been subject to recall bias.

Technical success and Ostial patency

In the study by Cutler *et al*. (2013), the technical success rate of balloon dilation was reported as 99.0% compared with 98.8% for FESS (no significant difference) [2].

In the 12 month study by Bikhazi *et al.* (2014) [3], 88/91 (96.7%) ostia were reported as patent in the balloon group, compared with 77/78 (98.7%) in the FESS group (no statistically significant difference). These figures are at slight variance to those published in the submission which were 91.9% (124/135) and 97.4% (111/114) respectively (no statistically significant difference) based upon data reported by Chandra *et al*. (2016) [4].

Work productivity and activity

The study by Bikhazi *et al.* (2014) [3] reported that both treatments had positive effects in all the domains of the WPAI survey, with the exception that FESS did not significantly improve the absenteeism domain ($p = 0.169$), although there was an absolute reduction. These data were presented in the submission as percentage reductions but the EAC could not repeat the calculations from the study report.

Complications and revision therapy

The number of complications was reported as zero in both arms of the REMODEL study [3]. One patient in each arm required revision treatment after 1 year, which was described in the original paper [2]. An additional patient was recorded as requiring treatment in the FESS arm at 18 months [4]. Thus there was no statistically significant difference between arms.

3.6.3 Results of observational studies

The observational studies provided longitudinal data that measured the outcomes before and after treatment with balloon dilation. These results are supplementary or supportive to the comparative efficacy data, and are particularly useful in the measurement of technical success, safety outcomes and change in QoL.

All of the observational studies measured changes in patient symptoms (SNOT-20) as a primary outcome. These results together, with those of

recovery outcomes, nasal debridements, healthcare utilisation and work productivity (WLQ), have been synthesised in a published meta-analysis supplied by the company, and are discussed in Section 3.8. Key results from the individual studies, considered relevant by the EAC, are briefly discussed in the following sections.

XprESS Multi-Sinus Study

The results of the XprESS Multi-Sinus Study by Gould *et al.* (2014) [6] were correctly reported in Table B7.24 of the company's submission. The authors of the study reported a statistically significant and clinically meaningful improvement in the primary outcome, change in mean SNOT-20 score at 12 months compared with baseline, of -1.57 ($p < 0.0001$). At 12 months there were also statistically significant reductions in the RSI major symptoms score; medication use (ICS, antihistamines, antibiotics); work or school days missed; and acute sinus infection and sinus-related physician visits. The authors reported that the procedure was a technical success in 307/313 sinuses operated on (98.1%), with only 1 patient requiring revision at 12 months (1.3%), and no serious device or procedural adverse events were reported. The procedure appeared to be well tolerated (mean pain VAS 2.8 ± 2.2) with a high degree of patient satisfaction (87.8%).

This study was notable in that it performed subgroup analysis of treatment of different sinuses. In the study, 22 patients underwent maxillary, frontal, and sphenoid balloon dilation; 32 patients underwent maxillary and frontal balloon dilation; 5 patients underwent maxillary and sphenoid dilation; and 22 underwent maxillary dilation only. The authors reported that the primary outcome (reduction of mean SNOT-20 score by at least 0.8 points) was achieved in 86.4% of patients who had multisinus dilation of the maxillary, frontal, and sphenoid ostia. This compared with 77.9%, 80.0% and 71.4% in the maxillary-frontal, maxillary-sphenoid, and maxillary only subgroups respectively. There was a statistically significant and clinically meaningful reduction in the mean SNOT-20 scores from baseline to 12 months in each subgroup combination of sinuses treated. In addition, there was a large, statistically significant improvement as measured by Rhinosinusitis Symptom Inventory (RSI), and significant reductions in number of antibiotic courses, physician visits, and acute sinus infections observed in all the subgroups.

The study also found statistically significant and clinically meaningful reductions in SNOT-20 scores at 1-year among the following subgroups: CRS vs RARS; baseline LM scores; presence of absence of ethmoid disease; septal deviations; and turbinate reductions. The subgroup comparisons reported in the XprESS Multi-Sinus Study provide some evidence that the XprESS MSDS is effective at providing significant and important symptomatic

improvement in all the sinuses it is indicated for use in, and thus indicates that results from the REMODEL study may be generalisable to a somewhat broader population.

XprESS registry

The XprESS registry by Brodner et al. (2013) [33] used hybrid balloon and FESS surgery as the intervention in the large majority of patients (156/175), with 10 patients not receiving balloon dilation, and 9 patients receiving only standalone balloon treatment. The company reported the results of the study in Table B7.25 of the submission. As these results were not disaggregated, the results from this study could not be applied to the decision problem and were not included in the meta-analysis [4]. However, results were similar to the other observational studies employing standalone balloon dilation only, including statistically significant reductions at 12 months in SNOT-20 score (-1.1), medication use, work or school days missed, sinus-related physician visits. There was no significant reduction recorded in the post-procedural occurrence of acute sinus infections, and no serious adverse events reported. Technical success was 96% (479/497 sinus procedures).

XprESS Maxillary Pilot Study

The XprESS maxillary pilot study by Gould (2012) [8] reported a statistically significant and clinically meaningful reduction in mean SNOT-20 score of -1.5. All sinuses operated on were a technical success (42/42), with no adverse events recorded. Other outcomes were non-comparative and are listed in the company's submission in Table B7.26.

RELIEF Study

The RELIEF study by Levine et al. (2013) [9] investigated the use of standalone FinESS as the intervention in patients with CRS or RARS, with most outcomes reported 1 year post-procedure (reported in Table B7.28 of the submission). The authors reported a significant and clinically meaningful reduction in SNOT-20 score (-1.2) compared with baseline. Subgroup analysis demonstrated no statistically significant differences in reductions in SNOT-20 scores between patients with maxillary only and patients with maxillary and anterior ethmoid disease. Additionally, statistically significant reductions in RSI major symptoms; medication use (ICS, antihistamines, antibiotics); absenteeism; sinus-related physician visits; and acute sinus infections were reported. The procedure was reported as a technical success in 91.9% of sinuses operated on (124/135) with a revision surgery rate of 5.8% (4/69 patients). No serious adverse events were reported.

BREATHE Study

The BREATHE study was conducted using the FinESS system as the intervention [10-12]. The authors reported the primary outcome in this study, reduction in SNOT-20 score, showed a statistically significant and clinically meaningful improvement compared with baseline after 1 year (-1.80) and 2 years (-1.86) follow up. At 1 year there was also a significant reduction in WQL and WPAI compared with baseline. The technical success rate was reported as 97.7% (129/132 sinuses). Procedures were well tolerated with a mean pain VAS of 2.7, with 88% of patients reported to have recovered within 2 days, and a patient satisfaction rate of 89% after 1 year and 91.5% after 2 years. After 2 years, 4/59 patients (6.8%) required revision surgery. One patient was reported as having suffered a serious procedure-related adverse event following balloon dilation (subcutaneous emphysema).

3.6.4 Relating the evidence to the decision problem

The statement of the decision problem (Table A1.1 of the company submission) listed several patient and healthcare outcomes. In Table 3.6, the EAC has reported how these outcomes were specifically addressed by the evidence reported by the company in the clinical submission.

Table 3.6: How outcomes in the scope were addressed by the evidence in the company submission

	Outcome	Is outcome measured in included studies?	Direction and magnitude of effect.	Relevant studies
Patient Outcomes	Change in rhinosinusitis symptoms (Sinus nasal outcome test [SNOT version 20 or 22] or RSI.	Yes, SNOT-20 was the primary outcome of all the included studies. RSI was reported in 2 observational studies	Statistically significant and clinically important reduction in SNOT-20 compared with baseline at up to 2 years follow-up (see Section 3.6.2) No significant difference in SNOT-20 score compared with FESS at any time point. Significant reductions in RSI compared with baseline.	REMODEL trial [2-4] XprESS Multi-Sinus Study [6] XprESS Registry [7] XprESS Maxillary Pilot Study [8] RELIEF Study [9] BREATHE Study [10, 12]
	Number of post-procedure rhinosinusitis episodes requiring medication	Yes, number of rhinosinusitis episodes recorded pre- and post-procedure in REMODEL study (but requirement for medication not specified). Similar outcomes some observational studies.	Large significant reduction in post-procedural episodes in both balloon and FESS arms. No statistically significant difference between arms (reduction of 4.2 and 3.5 episodes per year for balloons and FESS). Observational studies show significant decreases in related outcomes (e.g. reduction of 3.9 ± 4.5 acute infections of nose or sinuses in meta-analysis).	REMODEL Study [3] XprESS Multi-Sinus Study [6] XprESS Registry [7] RELIEF Study [9]

	Number of post-operative debridements	Yes, measured in REMODEL study (described as primary outcome) and 1 observational study	Mean number of post-procedure debridements per patient was statistically significant lower in the balloon arm compared to FESS (0.1 versus 1.2; p<0.001). Similar low rate in meta-analysis (0.16 ± 0.55).	REMODEL Study [2] BREATHE Study [12]
	Change in ostial patency (assessment of sinus drainage pathway patency by endoscopy or CT scan)	Yes, measured in REMODEL study.	No statistical significant difference in ostia patency after 1 year follow-up between balloon arm and FESS (96.7% vs. 98.7%) Ostial patency of 90.6% reported at 3-months in the BREATHE study.	REMODEL Study [3] BREATHE Study [12]
	Duration of analgesic medication	Yes, measured in REMODEL study and 1 observational study	Significant reduction in number of days on prescription pain medications with balloon (0.9 versus 2.8 days; p<0.001) and fewer days on over the counter analgesia (1.6 versus 2.7 days; p = ns)	REMODEL Study [2] XprESS Maxillary Pilot Study [8]
	Patient-reported tolerance of the procedure and/or patient reported severity of pain scale	Tolerance of procedure reported in most observational studies.	Absolute measurements only (no comparator) Mean VAS of 2.6 in meta-analysis.	XprESS Multi-Sinus Study [6] XprESS Maxillary Pilot Study [8] RELIEF Study [9] BREATHE Study [10, 12]

	Number and types of sinuses treated	Subgroup analysis in 1 observational study	No difference in outcomes between maxillary, frontal, sphenoid subgroups.	XprESS Multi-Sinus Study [6]
Health care system outcomes	Length of hospital stay	Not reported.		
	Procedure time and theatre/outpatient treatment room time	Not reported.		
	Success rates of maxillary sinus ostial cannulation	Technical success (which was on maxillary sinuses) reported in REMODEL study. Technical success reported in all observational studies.	No significant difference in technical success in balloon groups compared with FESS (99.3% vs. 99.4%). 97.5% technical success in meta-analysis.	REMODEL Study [2, 4] XprESS Multi-Sinus Study [6] XprESS Registry [7] XprESS Maxillary Pilot Study [8] RELIEF Study [9] BREATHE Study [10, 12]
	Rate of revision surgery	Yes, rate of revision was reported in REMODEL study and all observational studies.	Rate of revision low in all studies, no statistically significant difference between balloon and FESS arms (1.4% vs. 1.7% after 1 year). Revision rate 3.2% in meta-analysis.	REMODEL trial [2-4] XprESS Multi-Sinus Study [6] XprESS Registry [7] XprESS Maxillary Pilot Study [8] RELIEF Study [9] BREATHE Study [10, 12]
	Number of sinus-related follow-up appointments	Yes, outcome specified in several observational studies.	Meta-analysis reported reduction of 4.5 ± 11.5 visits to nurse/physician post-procedure.	XprESS Multi-Sinus Study [6] XprESS Registry [7] RELIEF Study [9]

	Rate of readmission	Not reported.		
	Numbers and grade of staff required	Not reported.		
Adverse effects	Rate and severity of nasal bleeding	Not directly reported. Nasal bleeding at discharge reported in REMODEL study.	Rate of bleeding at discharge significantly higher in patients who had received FESS compared with those receiving balloons (28% versus 55%; p=0.011) In the meta-analysis, 13.8% (32/232) of balloon dilation patients reported nasal bleeding after discharge.	REMODEL Study [2]
	Device-related adverse events	All studies reported on device related adverse events.	In REMODEL study, no serious adverse events reported in either arm. Among all the balloon dilation studies included in this report, there has been 1 potentially serious device-related adverse event reported in the BREATHE study.	REMODEL trial [2-4] XprESS Multi-Sinus Study [6] XprESS Registry [7] XprESS Maxillary Pilot Study [8] RELIEF Study [9] BREATHE Study [10, 12]

The EAC considered that the company, through their submission of clinical evidence, had adequately addressed many of the outcomes specified in the scope. The company had demonstrated that, in a relatively highly selected population that may not be fully equivalent to those treated in the English NHS, XprESS MSDS was non-inferior to FESS in improving patient symptoms and QoL up to 2 years. XprESS MSDS was also statistically equivalent to FESS in maintaining ostia patency and demonstrated a similar low requirement for surgical revision, improved work productivity, reduction in rhinosinusitis symptoms, and low frequency of adverse effects. There was some evidence that XprESS MSDS reduced short-term recovery times and the need for analgesia compared with FESS. The REMODEL trial also suggested that XprESS MSDS was associated with a reduction in the need for debridement; however this outcome may be of less relevance in an NHS setting (see Section 2.1.2).

The EAC considered that the clinical evidence in the submission did not address some of the outcomes concerning resource use. This included length of hospital stay, procedure time and theatre time, numbers and grade of staff, and rate of readmission. These are important outcomes that inform the economic analysis (see Section 4).

The EAC considered how the presented clinical evidence addressed the claimed benefits made by the company in the briefing note; these are summarised in Table 3.7. The EAC considered that the principal claim of equivalence of XprESS in terms efficacy, coupled with reduced inflammation and associated management in the short-term, were plausible and substantiated (with the caveats of generalisability). However, the EAC judged that many of the claimed healthcare benefits, which are important for the economic analysis, were not supported by clinical evidence. In general this was because there was a lack of evidence, rather than negative evidence.

Table 3.7: Evidence of claimed benefits of company

	Claimed Benefit	Evidence for benefit
Patient benefits	Offers a minimally invasive alternative to FESS with equivalent efficacy, which preserves more sinus tissue and mucosa with minimal acute inflammation	REMODEL showed XprESS non-inferior to FESS in terms of primary outcome (SNOT-20 score) in selected patients up to at least 2 years follow-up. Indirect short-term evidence indicates acute inflammation reduced compared with FESS. No evidence on sinus tissue preservation but mechanistically plausible.
	Reduction in risks associated with general anaesthesia as the procedure is undertaken while the patient is awake and under local anaesthesia	No direct evidence from studies supplied. However, plausible if general anaesthesia can be avoided.
	Faster recovery time with less nasal bleeding and shorter duration of need for pain medication.	REMODEL demonstrated reduced nasal bleeding and reduced prescribed (but not OTC) analgesia of XprESS MSDS compared with FESS.
	Improved patient comfort and tolerance compared with other balloon technologies, as XprESS allows more control of device placement	No evidence reported to substantiate this claim.
	More accurate cannulation of the maxillary ostium.	No evidence reported to substantiate this claim. [unclear how this is a patient benefit]
Healthcare system benefits	Reduction in theatre time compared to FESS (estimated to be a reduction of 60 minutes based on physician feedback)	No objective evidence reported to substantiate this claim.
	Reduction in staff numbers required as the XprESS procedure can be carried out in a day surgery setting under local anaesthetic rather than a main operating theatre under general anaesthetic	No objective evidence reported to substantiate this claim.
	Reduction in length of stay	Not directly shown by evidence. Comparative evidence from REMODEL study reported significantly reduced recovery time.
	Reduction in duration of prescription pain medication	REMODEL study demonstrated reduced prescribed analgesia with XprESS MSDS.
	Reduction in post-operative nasal bleeding visits	No objective evidence reported to substantiate this claim.
	Reduction in hospital readmissions.	Not substantiated. No significant

		difference between revision rates in REMODEL trial.
	Potential for a reduction in the number of patients waiting 18 weeks or longer for ENT surgery since the procedure allows for greater patient throughput	No objective evidence reported to substantiate this claim.
	Ease of use compared with other balloon technologies as the XprESS is based on a sinus seeker and no guidewire is needed.	No objective evidence reported to substantiate this claim.
Sustainability benefits	Improved resource utilisation due to a quicker procedure time and fewer complications	No evidence reported to substantiate this claim. No information on procedure times supplied and no evidence complication rates lower.
	Reduction in components and packaging waste due to ability to treat all sinus types with a single device.	No evidence reported to substantiate this claim. The XprESS system is single use meaning components such as PathAssist will be discarded after a single use.

3.6.5 Company's interpretation of clinical evidence

The company provided an interpretation of the clinical evidence in Section 7.9 of the submission. In Section 7.9.1, the company provided a broad overview of the evidence base and the results it provided. The EAC agreed with this assessment. The company concluded with the following statement:

> "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".

The EAC would agree that the clinical and safety evidence provided is generally supportive of the use of XprESS MSDS as an alternative option to FESS in selected patients with CRS. However, as discussed, the EAC would caution that the current comparative evidence base for XprESS is limited in terms of power at later time points and there may be issues with generalisability.

The company summarised their interpretation of the strengths and weaknesses of the evidence base in Section 7.9.2 of the submission. The company described weaknesses caused by the lack of blinding in the REMODEL trial, the use of hybrid surgery in some patients, and the lack of data on treatment of sinuses other than the maxillary or anterior ethmoid

sinus. The EAC agrees with the company on these points but has noted other weaknesses (see Section 3.5 of this report for critical appraisal and discussion in Section 3.10).

In Section 7.9.3 of the submission, the company discussed how the evidence relates to the scope. The EAC agrees that in general the evidence base reported was relevant to the scope. However, the company claimed the clinical evidence included analysis of patients with and without nasal polyps. The only study which reported this comparison identified by the EAC was the XprESS Registry by Brodner *et al.* (2013) [7]. The principal intervention used in this study was mainly hybrid surgery, not standalone balloon dilation. In the opinion of the EAC this invalidates the results of this comparison. The EAC considered the lack of data on the effect of balloon dilation on nasal polyps was a major weakness of the evidence base.

The company discussed the external validity of the supplied evidence in Section 7.9.4. The EAC has discussed limitations of generalisability in Section 3.5.3.

The company discussed the patient selection criteria of the included studies in Section 7.9.5. The EAC agrees that the selection criteria was generally well described in the studies and consisted of "*patients with uncomplicated CRS who meet the criteria for medically necessary FESS*". However, the EAC had remaining concerns that the definition of medically necessary FESS may be different in practice in the US, where all the studies were conducted, and the NHS.

3.7 *Description of the adverse events reported by the company*

The selection of clinical evidence by both company and EAC excluded case reports. Whilst conducting the primary literature sift against the selection criteria, the EAC made a note of any case reports that were specifically reporting adverse events from balloon dilation. Five case reports were identified by title and abstract; 2 were case reports of an adverse event arising from a different balloon technology and in the other 3 reports the device was not stated. No additional case reports of adverse events were identified during the sift of records from the additional EAC literature search strategy.

In Section 7.7.2, the company reported that 1 serious procedurally-related adverse event was reported in the selected studies; this was in a patient enrolled to the BREATHE study who received treatment with the FinESS system [10]. The patient suffered from subcutaneous emphysema (facial swelling) after resuming continuous positive airway pressure following the procedure, and recovered with a week. The EAC notes that there were no device related adverse events recorded in the REMODEL trial or the other observational studies.

The FDA MAUDE database houses reports on medical devices which have been submitted to the FDA because of suspected device-associated deaths, serious injuries and malfunctions. Reports are submitted by mandatory reporters such as manufacturers, importers and facilities where the devices are used as well as voluntary reporters such as health care professionals, patients and consumers. It should be noted that the MAUDE database is a passive surveillance system and potentially includes incomplete, inaccurate, untimely, unverified or biased data. The incidence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device used.

The EAC conducted a search of the FDA MAUDE database for the term “Entellus” from 01/01/2009 to 29/02/2016 and identified 12 reports in total.

Of 8 reports on the “XprESS Multi-Sinus Dilation Tool”, 6 were reports of cerebral spinal fluid (CSF) leak, comprising: balloon only procedures (n=2), balloon with septoplasty (n=2) and hybrid endoscopic sinus surgery (ESS) procedures (n=2). No report noted any long term adverse health effects as a consequence. One report was the case of orbital wall damage described by the company in Section 7.7.3 of their evidence submission. This case was reported to have had no long term adverse effect on the patient’s vision. The eighth reported case was a death from massive intracranial bleed, shortly after successful completion of a bilateral maxillary balloon procedure. The clinicians involved reported that this bleed was unrelated to device or procedure.

2 reports on the “XprESS LoProfile Multi-Sinus Dilation System” were a CSF leak during a hybrid ESS procedure and a device malfunction (light failing to turn on).

1 report on the “PathAssist Light Fiber” was a case where an audible “pop” was reported by the clinician, followed by CSF leak. The balloon itself had not been deployed on this occasion.

1 report on the “Entellus Medical FinESS Sinus Treatment” was swelling of the face and neck after the patient was put onto continuous positive airway pressure (CPAP) on the evening of the procedure. This has been confirmed as being the same event reported by the company in Section 7.7.2 of their evidence submission [10].

3.8 *Description and critique of evidence synthesis and meta-analysis carried out by the company*

3.8.1 Description of methodology

The company reported a meta-analysis of the published studies in their submission. This evidence synthesis was published as part of the paper by Chandra *et al.* (2016) [4] and combined the results of the REMODEL study with several of the observational studies. Evidence synthesis of observational data to boost power is now commonly performed [60]. The methodology of the meta-analysis was described by the company in Section 7.8.1 of the submission document.

The study by Chandra did not include a systematic review of the evidence base; therefore a full critical appraisal of the study using a checklist is not appropriate. Instead, the authors selected studies on dilation using balloons manufactured by Entellus Medical that were already known to them; that is, the studies discussed in the submission and this report. The EAC has confirmed though its own literature searches that there are unlikely to have been any studies omitted using this approach.

The authors had access to the original patient data from Entellus Medical which meant that an individual patient data meta-analysis could be performed. This is generally regarded as superior compared with meta-analysis of summary statistics [61]; however it meant that the EAC were unable to replicate the results. The number of patients contributing to each outcome and time point was clearly tabulated in the published paper. The author employed suitable statistical methods to report the descriptive and comparative statistics, and used random-effects modelling. This is an appropriate conservative methodology when there is heterogeneity present in the contributing studies [62].

The main limitation of the meta-analysis resulted from the primary studies themselves. With the exception of the REMODEL trial [2-4], which was described in terms of balloon and FESS arms, the studies were all single armed observational studies, namely the XprESS multi-sinus study [6], the XprESS maxillary sinus study [8], the RELIEF study [9], and the BREATHE study [2, 12]. The XprESS registry [7] was correctly excluded as it reported data from patients undergoing hybrid surgery which could not be disaggregated. As these studies did not report comparative data, neither did the meta-analysis (with the exception of SNOT-20 scores, see below). Instead results were reported as single point measurements (without distributions), or were compared with baseline (pre-procedural) data.

3.8.2 Description of results

Short-term outcomes

In Table B7.32, the company listed the results of short-term outcomes. As these were by definition post-procedural, they were reported as absolute measurement and could not be contextualised against a baseline.

These have been reported in Table 3.6 where they have matched outcomes specified in the scope.

SNOT-20 scores

Figure B7.2 of the company's submission charted pooled, longitudinal data illustrating the improvement in mean SNOT-20 score from baseline to 1 week, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months. The graph clearly shows an immediate overall benefit after 1 week, which then plateaus and persists for up to 2 years. Furthermore, there were clear benefits demonstrated in each of the subscales (rhinologic, ear and facial, sleep function, and psychological). The company stated that "SNOT-20 scores were statistically significant, clinically meaningful, and durable through 24 months".

The pooled SNOT-20 data from the observational studies is reported in Table 3.8 (data taken from original paper). The authors reported that there was no statistical difference in the SNOT-20 outcome between studies (REMODEL FESS, REMODEL balloon dilation) or pooled observational studies). Additionally, the effect size seemed to be consistent between the observational studies (illustrated in the original paper).

Table 3.8: Changes in mean SNOT-20 scores compared with baseline in REMODEL and observational studies. Data taken from Chandra *et al.* (2016) [4]

	Time period		
	6 months	**12 months**	**24 months**
REMODEL FESS arm*	-1.60 (59)	-1.60 (58)	-1.45 (10)
REMODEL balloon dilation arm*	-1.56 (72)	-1.59 (69)	-1.65 (15)
Pooled single armed studies*	-1.36 (255)	-1.49 (241)	-1.86 (59)
P value (F test) **	0.199	0.682	0.482

Number of patients in each cohort in parenthesis. Note that patient numbers from REMODEL trial is from larger cohort as described by Chandra *et al.* (2016) [4].
* All values significantly different than baseline ($p < 0.0001$).
** Comparison of mean change between studies.

XprESS vs. FinESS

The contributing studies to the meta-analysis used both the XprESS MSDS and its predecessor, the FinESS system. Specifically, the REMODEL trial [2] used a combination of systems; the XprESS Multi-Sinus study [6] and XprESS Maxillary Pilot study [8] used XprESS MSDS exclusively; and the RELIEF Study [9], the BREATHE study [10, 12], and the FinESS study [13] used the FinESS system exclusively.

The authors of the meta-analysis did not use the individual patient level data to make a formal comparison of the 2 balloon techniques. However, a comparison of summary data from the observational studies, illustrated in Figure 4 of the published paper, does not show any obvious dissimilarity between studies using the different techniques. This provides some reassurance of equivalence between the 2 methods (see Section 2.3.2).

Other outcomes

The meta-analysis reported changes in the RSI, which was an outcome specified in the scope. The results are reported in Table B7.33 of the submission and have been reported in Table 3.6 where they are relevant to the scope. In summary, there were statistically significant reductions ($p < 0.0001$) from baseline compared with 12 months in the domains of work/school missed due to nasal problems (-5.0 days ± 9.5 [SD]); homebound

due to nasal problems (-6.3 days ± 11.3); number of physician/nurse visits due to nasal problems (-4.5 visits ± 11.5); number of infections of nose/sinuses (-3.9 episodes ± 4.5); and number of antibiotic courses (-2.9 courses ± 3.1).

The meta-analysis reported changes in the Work Limitations Questionnaire (WLQ) over at 1 week, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months compared with baseline. This was presented as a longitudinal graph in Figure B7.3. There were statistically significant and immediate reductions in the domains of time management, physical, mental/interpersonal, output, and productivity loss, which appeared maximal at 1 month before plateauing over 2 years.

The meta-analysis also provided data on revision rates at 12 months, which were 1.7% for the FESS arm of the REMODEL trial, 1.4% for the balloon dilation arm of the REMODEL trial, and 3.2% for the pooled analysis of the single armed observational studies. There was no statistically significant difference between these data sources (p = 0.628). However, this analysis was based on very low event numbers (a single patient in each of the REMODEL arms).

3.8.2 Conclusion of meta-analyses

The company provided synthesised individual patient data from the relevant observational studies included in the submission. These data provided longitudinal analysis that demonstrated balloon dilation was associated with significant improvement in QoL, as measured by the SNOT-20 score, and improvements in symptoms, as measured by RSI. In both cases, the benefits appeared to be rapid (appearing after 1 week) and relatively long-lasting (up to 2 years). The reductions in SNOT-20 scores were consistent with those seen in both arms of the REMODEL trial.

Whilst the data from the meta-analysis should be treated with caution as it was non-comparative, the EAC considers that it adds support to the claims made by the company.

3.9 *Additional work carried out by the External Assessment Centre in relation to clinical evidence*

No additional work was undertaken.

3.10 *Conclusions on the clinical evidence*

In the opinion of the EAC, the company's submission of clinical evidence was of high quality and adequately addressed the decision problem stated in the scope. In particular, the submission was well written and consistently answered the questions posed in the template. The company identified and accurately reported the currently available published evidence on balloons indicated for dilation manufactured by Entellus Medical (i.e. the XprESS MSDS and FinESS systems). The EAC did not identify any omitted studies from its independent literature searches, and whilst the possibility of publication bias cannot be completely ruled out, it is likely that all the available relevant evidence was assessed.

The EAC considered that the best evidence on clinical effectiveness was derived from the REMODEL trial. This was an RCT that compared XprESS MSDS (or its predecessor, the FinESS system) with FESS in adult patients with CRS or RARS caused by maxillary sinus disease with or without anterior ethmoid disease. Each patient also met the criteria for medically necessary FESS for uncomplicated rhinosinusitis according to US medical insurance criteria [2-4]. This study design was assessed by the EAC as being of high methodological quality. The internal validity of the study was generally good, but was diminished by the high initial attrition rates in the FESS arm immediately following randomisation, and the subsequent requirement for post hoc modified ITT analysis. The EAC was satisfied that the evidence showed balloon dilation was non-inferior to FESS in terms of the primary outcome (measurement of QoL using the SNOT-20 score).The improvement of QoL in both arms continued for a time period of up to 2 years post-procedure. The EAC also judged the evidence demonstrated that balloon dilation was equivalent to FESS over this time frame in terms of the secondary outcomes measured, such as maintaining ostia patency, reducing future episodes of rhinosinusitis, and improving work and productivity. Furthermore, there was evidence that balloon dilation offered advantages over conventional FESS by speeding recovery, reducing post-operative pain and reducing the requirement for nasal debridement and post-discharge nasal bleeding.

The EAC considered the main limitation of the REMODEL study was the relatively low patient numbers (to evaluate longer-term and secondary outcomes) and potential biases caused by the unavoidable lack of blinding and relatively large absolute dropout in the FESS arm, resulting in loss of randomisation.

The clinical evidence reported by the REMODEL study was supplemented by several, single armed, observational studies that investigated the use of

XprESS MSDS [6-8] or the FinESS system [9, 10, 12] in patients with CRS or RARS. Results from these studies, with the exclusion of the XprESS registry [7], which featured hybrid rather than standalone dilation, were combined in a published meta-analysis [4]. Whilst these studies did not provide additional comparative data with FESS, they did provide supportive longitudinal data that indicated the use balloon dilation was associated with an important and persistent (up to 2 years) improvement in QoL as measured by SNOT-20, and improvements in other patient related outcomes such as reduced time of absence from work or school.

The EAC considered the primary difficulty in how the clinical evidence from the trial and observational studies informed the decision problem concerned the external validity of the data; that is, the generalisability of the evidence to NHS practice. The key concerns for the EAC were:

- Whether the patients enrolled had equivalent refractory CRS comparable with patients undergoing surgery in the NHS, as discussed in Section 3.5.3.

- The impact of nasal polyps on treatment effect, which was not adequately explored in any of the studies that investigated the use of standalone balloon treatment. Up to two thirds of patients presenting to secondary care with CRS have nasal polyps [18].

- The comparative efficacy of balloon dilation used in different sinuses, as the REMODEL study was limited to patients with maxillary sinus disease with or without anterior ethmoid disease [2]. However, subgroup analysis used in the XprESS Multi-Sinus study was supportive that treatment is effective in all the sinus types [6].

- The functional equivalence of the XprESS MSDS and FinESS systems, as there was no direct comparative evidence identified to inform this uncertainty. However, data from the meta-analysis was consistent with equivalence [4].

In summary, the EAC considered the company provided evidence that the XprESS MSDS or FinESS system provide non-inferior patient benefits compared with FESS in selected patients with refractory CRS of RARS of the maxillary sinus with or without anterior ethmoid disease. This comparative evidence was supported by more extensive observational data which showed comparable longitudinal results. However, as this patient population represents a subgroup of those treated within the NHS, there is currently uncertainty whether the procedure would be as effective in all patients indicated for surgery within the NHS, and in particular there is uncertainty in

the efficacy of the procedure in patients with nasal polyps. Additionally, the evidence on the effectiveness of treatment other than the maxillary and anterior ethmoid sinuses was very limited. To reduce this uncertainty, further prospective research would be required (see Section 6). Nevertheless, the EAC considered that, these reservations aside, the company had substantiated the claims of clinical effectiveness as specified in the scope within the selected patient population.

4 Economic evidence

4.1 *Published economic evidence*

4.1.1 Critique of the company's search strategy

The Peer Review of Electronic Search Strategies (PRESS) Checklist (as described in Section 3.1.1) was used to inform the critique of the company's search strategies [40].

Search reporting

The MTEP Submission Template states that the review of economic evidence should be transparent and that the strategies used to retrieve relevant health economics studies from the published literature and unpublished data should be described. A description of the searches for published studies was given in the submission (Section 8.1.1. and Section 10.4). No description is given of any search for unpublished studies. The description of the search methods for identifying published studies was given in some detail, though was not fully transparent. The search strategies for 3 sources (MEDLINE via Ovid, PubMed and Embase) were reported explicitly and in sufficient detail to enable quality assessment and reproduction, although some details were not given (for example, the syntax used to combine the different lines in the Ovid databases was not explicit, and the segment of Ovid MEDLINE and Embase searched was not stated). Search methods were not reported for CDSR or NHS EED however. The number given for 'total number of results downloaded' equalled the total from Ovid MEDLINE, PubMed, Embase and NHS EED only; it was therefore not clear if any records were found via CDSR, or if found, whether they were assessed.

Search sources

The submission stated that MEDLINE via Ovid, MEDLINE via PubMed, Embase, CDSR and NHS EED were searched. MEDLINE, Embase and NHS EED are core databases (although NHS EED only has value for identifying literature published up to the end of 2014, as indicated in the submission). Although the search included these core sources, the submission methods would have been enhanced by inclusion of a wider range of databases (for example an additional specialist economics resource such as the Cost Effectiveness Analysis (CEA) Registry, a source of health technology assessments such as the health technology assessment (HTA) Database, additional sources of conference abstracts, and supplementary search

approaches such as contact with topic experts). The company's search sources did not include EconLit, which is one of the minimum required resources for economic evidence searches stated in the NICE submission template.

Search strategy structure, search terms and syntax, search restrictions

The sections of the search strategies on the population and intervention concepts did not mirror the equivalent sections in the clinical evidence strategies; no rationale was given for this difference.

The reported strategies for Ovid MEDLINE, PubMed and Embase were clearly structured into search concepts. Search terms were grouped appropriately, though the syntax for line combinations was not made explicit in the reported Ovid strategies. Boolean operators were used appropriately in the Ovid MEDLINE and Embase searches. In the PubMed search, some Boolean operators were in lower case, rather than the upper case as is required in PubMed [63]. For this particular search however, the use of lower case letters in PubMed would have had no impact on result totals. The searches for each concept in the Ovid MEDLINE and PubMed strategies were constructed using explicitly specified subject headings and free-text searches; in the Embase search however, free-text terms were not included for the rhinosinusitis concept and subject headings were not explicitly specified for the economics concept. The use of truncation was mainly appropriate.

The strategies explicitly included key subject headings for the population of interest, and some of the key subject headings for the intervention of interest. Some potentially relevant subject headings were not explicitly included (for example the MeSH headings Dilatation/ and Catheterization/ in the Ovid MEDLINE and PubMed searches), but the non-specific approach taken to search fields for the free-text search lines (see below) meant that records indexed with these subject headings would have been retrieved anyway. No spelling errors were identified apart from the term 'exp balloon dilatation/' in the Embase strategy; it was judged that this error was a reporting error, rather than an error in the run searches.

The strategies included key free text terms for the population and interventions of interest. In some respects the company took a highly sensitive approach to the free-text searches (i.e. for the intervention concept, searching for all records which included the terms dilat*, balloon* or catheter*). This sensitive approach to the intervention terms would have increased the

likelihood of retrieving relevant studies (though at the expense of precision). In some other respects however, the range of free text terms, and the way they were used, had some limitations which could have increased the risk of missed relevant studies. For example, search methodology would have been enhanced by including potential free-text variants for sinusitis (such as sinus disease or sinus infection), by including the free-text terms 'sinusitis' and 'rhinosinusitis' in the Embase search (as the company did in the Ovid MEDLINE and PubMed searches), and by including search terms for the device trade name.

The company took a basic, non-specific approach to the use of search fields for the free-text searches; in Ovid the 'multi-purpose' (mp) syntax was used, whilst the PubMed search did not restrict by field. Although this approach meant the searcher had less control over the search, and although it was likely to decrease precision, it did also lead to relevant subject headings being covered by the search strategy even when not explicitly included. For example, although the Ovid MEDLINE and PubMed strategies did not explicitly include the relevant MeSH headings of Dilatation/ and Catheterization/ (as referred to earlier), the strategies would have retrieved studies indexed with these headings anyway, through the use of the 'multi-purpose' syntax.

For the section of the strategies intended to capture the economics concept, the company included some of the main relevant free-text terms. The use of the 'multi-purpose' (mp) syntax in Ovid and absence of field restrictions for the terms in PubMed also meant that the search would have retrieved records indexed with many of the main relevant subject headings, even though not all are specified in the strategy. However, the search would have been enhanced by including additional free text search terms, for example: costly, costing, price, prices, pricing, pharmacoeconomic, expenditure, value for money, and budget. In Embase, the reliance on the 'multi-purpose' syntax and lack of specified subject headings meant that the company's strategy did not include a search on relevant subject headings such as 'pharmacoeconomics/', 'health care financing/' or 'hospital purchasing'/. The use of a standard search filter designed to identify economic evaluations (such as that designed by the University of York Centre for Reviews and Dissemination to identify economic evaluations for inclusion in NHS EED, published online [64]), would have ensured that these relevant free text and subject heading terms were included in the company's searches and would have enhanced the submission methodology. By not using a filter designed to identify this type of evidence the company increased the risk of missed relevant studies. Given the very low number of records produced for screening, the inclusion of floating relevant

subheadings (Economics in MEDLINE and Pharmacoeconomics in Embase) would also have increased search sensitivity. There were inconsistencies across the different databases as to the search terms used for the economics concept. The Embase and PubMed searches for example, included free-text searches for terms such as model, models, modelling, modelling, whereas the Ovid MEDLINE search did not. No rationale was given for these differences.

The documented searches were restricted to studies published in English. This reflected the study selection criteria, although no rationale for the language restriction was found in the submission. The searches were also restricted to studies published from 2010. No rationale was found in the submission for the date restriction (the clinical evidence searches included studies published from 2006). The searches were carried out in February 2016 and as such had good currency at the time of submission. The company identified 134 records, 96 of which remained following deduplication.

Re-run company searches

The EAC could not fully reproduce all the company searches as strategies were not explicitly reported for the search of CDSR or NHS EED. The Ovid MEDLINE, PubMed and Embase search strategies were re-run as reported. For the purpose of the Ovid MEDLINE search, the EAC assumed that the company searched the following segment: Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE. The strategies used when re-running the company's search and the volume of results identified for each search source, are fully reported in Appendix 3. The searches as re-run by the EAC retrieved 90 records, with 55 unique records remaining after deduplication. This yield did not reflect the original company searches (where 124 records were retrieved from the same 3 sources). As some aspects of search methodology were not reported explicitly by the company, it was not possible to identify the reason for this difference in record numbers. It is possible that the difference related to the choice of segments searched in Ovid, or the way lines were combined, or the applications of language and date limits for example, but without explicit methodology it was not possible to be certain.

EAC's search strategy

The searches carried out by the EAC to identify clinical effectiveness evidence (reported in Section 3.1.1 and Appendix 2) were not restricted by study design and were prospectively designed to retrieve both clinical effectiveness and economic evidence. The sources searched included those

required as a minimum by NICE for the search on economic evidence as stated on the submission template (MEDLINE, MEDLINE In-Process, Embase, EconLit and NHS EED) and other additional databases as detailed in Appendix 2. These additional databases included a further specialist economic database (the CEA Registry) and the HTA Database. All results from these searches were assessed for relevance to the economic submission. No additional search for economic evidence was therefore carried out by the EAC.

The EAC's search retrieved 1,204 records, with 698 unique records remaining after deduplication. Full details of all the search resources and strategies used by the EAC search (including search date and the volume of results returned) are provided in Section 3.1.1 and Appendix 2.

4.1.2 Critique of the company's study selection

Company's study selection

During study selection the company adopted a PICO framework, which was the same approach taken to select clinical studies. However, the PICO criteria (see Section 8.1.1 of the company's submission) adopted for the economic selection was broader that those adopted to select clinical studies (Table B7.1 of the submission).

Both the company's clinical and economic reviews included studies reporting on the following intervention: "balloon sinus dilation using the XprESS Multi-Sinus Dilation System or equivalent". In the clinical evidence review, "or equivalent" was applied by the company to mean previous devices manufactured by Entellus. However, in the economic evidence review, "or equivalent" also included balloon dilation systems manufactured by other companies, for example Acclarent. The EAC judged that those studies not including either XprESS MSDS or its predecessors are outside of the scope specified by NICE. FESS was accurately required as a comparator intervention. However, the company omitted other balloon dilation systems as a comparator having already included these as a potential intervention.

The company applied broad inclusion criteria to the study design required for selection, whereby any study including cost data was included. Inclusion of a broad range of studies may have been beneficial in informing the company's *de novo* model. An English language restriction and search dates of 2010 to present were applied. These search dates were narrower than those used within the clinical evidence submission of 2006 to present. The reasoning for this discrepancy is not reported.

EAC's study selection

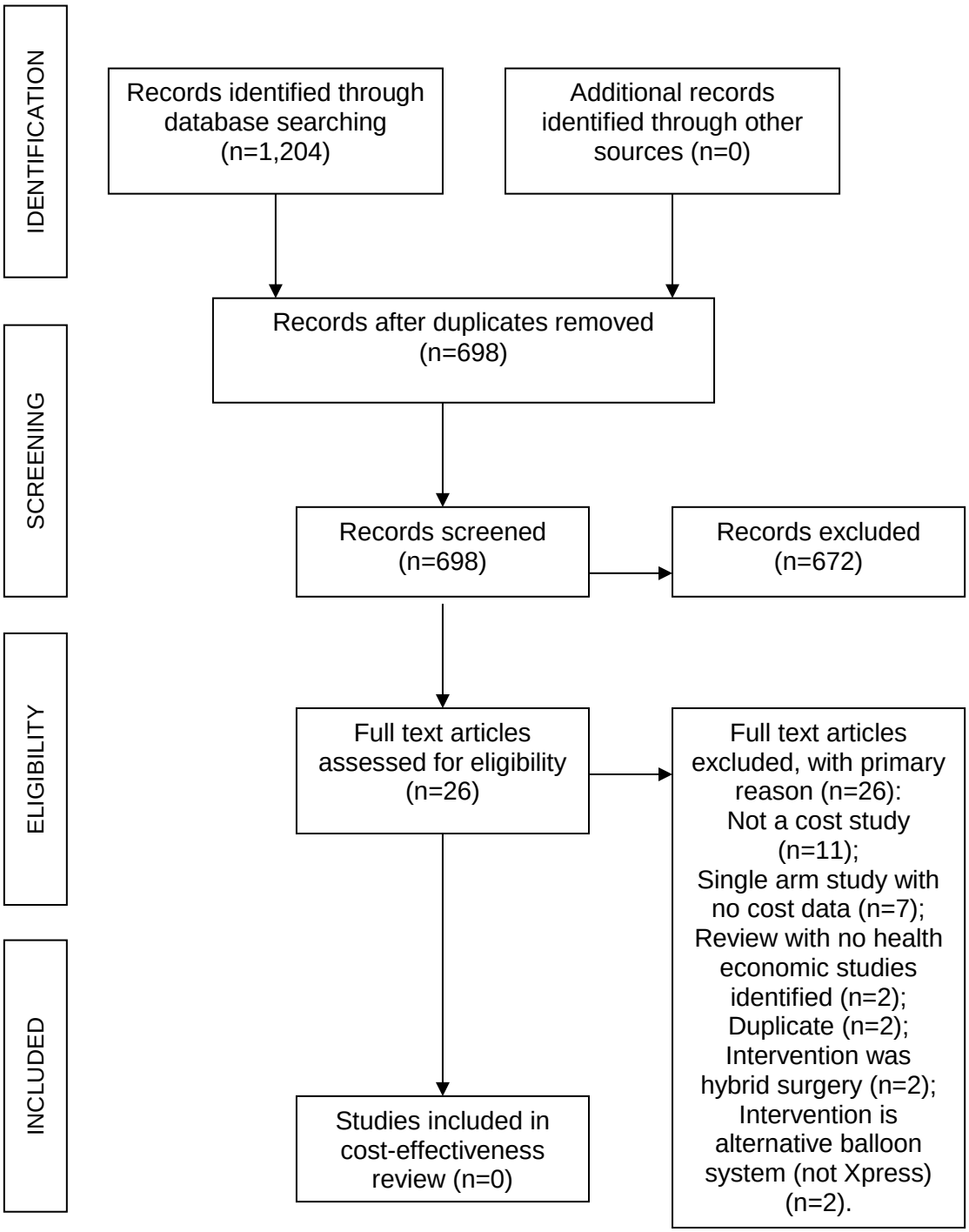
The selection criteria adopted by the EAC, to select relevant economic studies, are summarised in Table 4.1. These are consistent with the scope.

Table 4.1: Selection criteria adopted by the EAC for economic study selection

Inclusion criteria	
Patients	People with CRS (including children) People with RARS (including children)
Intervention	XprESS multi-sinus dilation system (any version – include FinESS system)
Comparator	FESS; Other balloon systems used within the NHS.
Outcomes	Not specified to maximise sensitivity
Study design	Heath economic studies (XprESS v. comparator): • Cost-effectiveness; • Cost-utility; • Cost-benefit; • Cost-minimisation; • Cost-consequence.
Language restrictions	English only
Search dates?	2006 - present
Exclusion criteria	
Population	Animal and in vitro studies; People with acute rhinosinusitis.
Interventions	Hybrid technologies (e.g. combination of balloon dilation and FESS); Other balloon systems.
Study design	Non-comparative cost analyses including cost of illness studies

The EAC applied the selection criteria listed in Table 4.1, to the literature search reported in Section 3.1. Only health economic studies reporting on XprESS MSDS or other balloon systems available on the NHS met the EAC's inclusion criteria as standalone economic studies of alternative balloon devices not available on the NHS are not informative in identifying the cost-effectiveness of XprESS MSDS compared with either FESS or other balloon systems used within the NHS. The study selection process is displayed in Figure 4.1. Reasons for exclusion at the full paper review stage are shown in Appendix 4.

Figure 4.1: PRISMA flow diagram showing studies assessed during EAC economic review



4.1.3 Included and excluded studies

Company's selected studies

The company included 6 of the 134 records identified, based upon their selection criteria. These studies are summarised in Table 4.2.

Table 4.2: Summary of company's included economic studies

Study and setting	Design	Population	Intervention	Comparator
Ference *et al.* (2015) [65]	Database analysis	Patients undergoing ESS or balloon dilation therapy	Balloon dilation with/without FESS (i.e. hybrid surgery in some cases)	FESS
Ference *et al.* (2014) [66]	Database analysis	Patients undergoing ESS and/or balloon dilation therapy	Balloon dilation with/without FESS (i.e. hybrid surgery in some cases)	FESS
Holy *et al.* (2013) [67]	Budget impact analysis	Patients with CRS	Potential surgical case mix with increase in balloon dilation therapy (Acclarent)	Current surgical case mix
McElroy *et al.* (2011) [68]	Systematic review	Patients with CRS	N/A – multiple studies were included with different interventions	N/A – multiple studies were included with different comparators
Smith *et al.* (2014) [69]	Systematic review	Patients with CRS	N/A – multiple studies were included with different interventions	N/A – multiple studies were included with different comparators
Sorgeloose *et al.* (2012) [70]	Budget impact analysis	Patients with CRS	Balloon dilation therapy with Acclarent device	FESS

The EAC replicated the company's literature review using the company's selection criteria and found that only 3 of the 6 studies should have been included: Sorgeloose *et al.* (2012); Ference *et al.* (2015) and Ference *et al.* (2014) [65, 66, 70]. The remaining studies should have been excluded on the following grounds:

- Holy *et al.* (2013) compared the present surgical case mix with future surgical case mix with an increase in balloon therapy, hence did not compare balloon therapy against FESS [67].

- McElroy *et al.* (2011) conducted a systematic review which did not meet the selection criteria in their entirety [68]. One of the included studies from that review by Freidman *et al.* (2008) would have been suitable for inclusion by the company had this study been published in 2010 or later, 2010 being the date limit set by the company [71].

- Smith *et al.* (2014) conducted a systematic review that did not meet the inclusion criteria in their entirety. Further, none of its included studies compared FESS against balloon therapy [69].

The EAC deemed that even the studies meeting the company's inclusion criteria could not answer the research question on the cost-effectiveness of adopting XprESS MSDS compared with current practice. Therefore the EAC excluded them as the study by Sorgeloose *et al.* (2012) reported on a device that is not available on the NHS (Acclarent) and the studies by Ference *et al.* (2014) and Ference *et al.* (2015) reported on hybrid surgery using non-specified balloon dilation devices which may not all be available on the NHS [65, 66, 70]. The studies are not discussed further within this section. However, the model structure reported in the study by Holy *et al.* (2013) was used by the company to inform their *de novo* model [67].

EAC's selected studies

No health economic studies were identified by the EAC as being relevant to the decision problem.

4.1.4 Overview of methodologies of all included economic studies

There were no economic studies included by the EAC.

4.1.5 Overview and critique of the company's critical appraisal for each study

The company reviewed each of its 6 studies individually using the quality assessment checklist adapted from Drummond and Jefferson (1996), a suitable checklist for assessing economic evaluation studies. Three of its

included studies were published at conferences only and therefore had limited information available to complete the checklist [67, 68, 70]. The included systematic reviews should have been critically appraised using a systematic review specific checklist [68, 69].

The results of the checklist were presented in tabular form within the submission and not discussed further. As such, the results of the review were not put into context within the narrative of the submission.

4.1.6 Does the company's review of economic evidence draw conclusions from the data available?

Company's conclusions

The company concluded no relevant high-quality evaluation or cost-effectiveness studies comparing XprESS MSDS to either FESS or other balloon dilations systems were available. This is an accurate conclusion.

EAC's conclusions

There was no relevant economic evidence presented by the company, or identified by the EAC, to inform the research question.

4.2 *De novo cost analysis*

The company created its own *de novo* cost model which was appropriate given the lack of UK based economic evidence available on the XprESS MSDS system. The structure of the model is now described.

4.2.1 PICO analysis

In this section, the population, or patients, technology, comparator and outcomes used in the model are described.

Patients

The company described the patients within the model as average risk patients attending for CRS surgery, where multiple sinuses are treated within 1 episode of care. Justification for the consideration of patients requiring multiple procedures was provided based on HES data. Expert advice sought by the EAC agreed that patients undergoing balloon dilation surgery would, on average, require treatment on multiple sinuses (correspondence log, appendix 1, collated responses, page 2).

Within the scope issued by NICE, a number of subgroups were listed for consideration. The company did not model these subgroups explicitly within their analyses, but rather assumed that the findings relating to an 'average risk' patient were generalisable to all subgroups.

Technology

The intervention considered in the model is the XprESS MSDS, which is consistent with the decision problem specified within the scope.

Comparator(s)

Two comparators were included within the model: FESS and treatment with the Acclarent balloon dilation system. The submission correctly focused on FESS as the key comparator to the XprESS system. A comparison to the Acclarent device was also included as the scope specified that other balloon systems in use within the NHS should be included as a comparator. However, the Acclarent device was withdrawn from the UK market on 31st December 2015 and is therefore no longer a relevant comparator (see correspondence log, appendix 3). The company and the EAC's experts specified alternative balloon systems that are used within the NHS (correspondence log, page 2 and NICE expert questionnaires). These are: Ventera sinus dilation system; LENIOflex; NuVent EM balloon sinus dilation system and Vent-Os sinus dilation system. No clinical evidence meeting the inclusion criteria relating to any of these devices was identified (Section 3). Further, the devices are not

listed on NHS supply chain and no publically available cost information relating to them could be obtained by the EAC through targeted searching. Therefore, the EAC judges that the company was correct to focus its analysis on comparing XprESS MSDS to FESS. The EAC's critique of model will focus on this comparison.

Outcome

The primary outcome is a comparison of the total costs of the 2 arms of the model. SNOT-20 scores are reported as a secondary outcome within the model supplied by the company, but are not included within the submission document.

4.2.2 Software

The company submitted a fully executable *de novo* model built in Microsoft Excel. The model comprised 13 worksheets. An overview of the content of each worksheet is now provided:

- 'COVER'. This sheet includes a title, information about the developers of the model and macro-enabled buttons to facilitate navigation through the model.

- 'INTRO_NAV'. The introduction sheet describes the contents of the model and the cell formatting used within the model to denote which cells can be modified and which cells cannot.

- 'INTRO_OV'. The model's objective is provided on this sheet.

- 'INTRO_STRUCT'. This sheet shows a diagram of the model structure as well as a description of the model and the key assumptions made within the model. The model structure and assumptions listed are consistent with those provided within the company's submission.

- 'INPUTS'. The inputs sheet of the model include all set up, clinical and cost inputs used within the model relating to XprESS MSDS, FESS and Acclarent. The model is set up so that those inputs not currently in use, for example those relating to Acclarent where FESS is selected as the comparator, are greyed out. The user of the model is able to overwrite cells with their own inputs and a 'reset all inputs to default' button allows the user to return to the company's base case inputs.

- 'REFS_&_ASSUMP'. This sheet lists all models inputs with a source and description or assumption of each. The current input value and default

input values are also displayed and any discrepancies highlighted through colour coding.

- 'RESULTS'. The results page reports the results of the model both in tabular and graphical format. The results are presented both as overall cost savings and as a breakdown by cost type. Cost differences over time are also presented. Finally, differences in outcomes for patients are presented including surgery time, risk of each outcome modelled and SNOT-20 score.

- 'DECISION TREE'. On this sheet the model's calculations are implemented for all 3 treatment options that are modelled. These comprise a decision tree, a Markov trace and a cost summary for each treatment option modelled.

- 'SA_INPUTS'. A written overview of deterministic sensitivity analysis (DSA) and the parameters and ranges evaluated are reported on this sheet. The user is able to vary the percentage increase or decrease of each input parameter. A macro enabled button allows the user to run the DSA which will update for user specified requirements.

- 'DSA_RESULTS'. The results of the DSA are presented via a tornado diagram on this sheet. The tornado diagram displays the change to net budget impact for each input that has been varied. The cost difference per patients based on the key driver of the model is also reported to highlight the range of plausible results of the model based upon the sensitivity analyses conducted.

- 'DSA_MECHANICS' and 'DSA_CALCS'. These sheets are 'back-end model sheets' that are used to generate the results of the DSA.

- 'GRAPHS'. The final sheet in the model displays graphs presenting threshold analyses around the length of surgery time with each treatment option. The break-even point is specified.

4.2.3 Structure

The *de novo* economic model produced by the company comprised a decision tree followed by a Markov model with 2 health states. The model has a 5 year time horizon with the first year costs being captured within the decision tree and the costs in years 2 to 5 being captured in the Markov model. The Markov model element of the model has a cycle length of 1 year. The company provided a largely accurate diagram of their model in Section 9.1.4 of the submission.

Within the decision tree element of the model, patients undergo sinus surgery following which they have either a general practitioner (GP) follow-up (within the first 3 months) or sustained recovery (no GP visit). All patients, regardless of their GP visit status are at risk of readmission to hospital. Furthermore, all patients regardless of their readmission status are at risk of revision surgery. The risk of revision surgery is not dependent on previous readmission to hospital or GP visits. Likewise, the risk of readmission to hospital is not dependent on prior GP visits.

Within the Markov model element of the model there are 2 health states: surgery revision and surgery success. An annual risk of revision surgery is applied to patients and those patients having revision surgery have a cost applied. Patients are not able to have multiple revision surgeries. Within the longer term element of the model, patients also have a background risk of GP visits for the medical management of acute exacerbations. This risk is independent of their revision status.

The EAC has provided an amended version of the model structure in Figure 4.2. This corrects a typographical error and expands on the diagram provided by the company so that all branches are displayed. This change has been made for ease of interpretation rather than to correct any errors in the company's model schematic.

The company reported that the model took an NHS perspective, but did not report the cost year of the analysis.

The company justified its choice of model structure by stating that it was designed to capture those outcomes in a UK real world setting as reported in the national audit of CRS surgery that impacted on resource use [15]. The model structure was identical for XprESS MSDS, FESS and Acclarent, as balloon dilation systems are a direct replacement of FESS in certain patients. This is explained in more detail in Section 2.

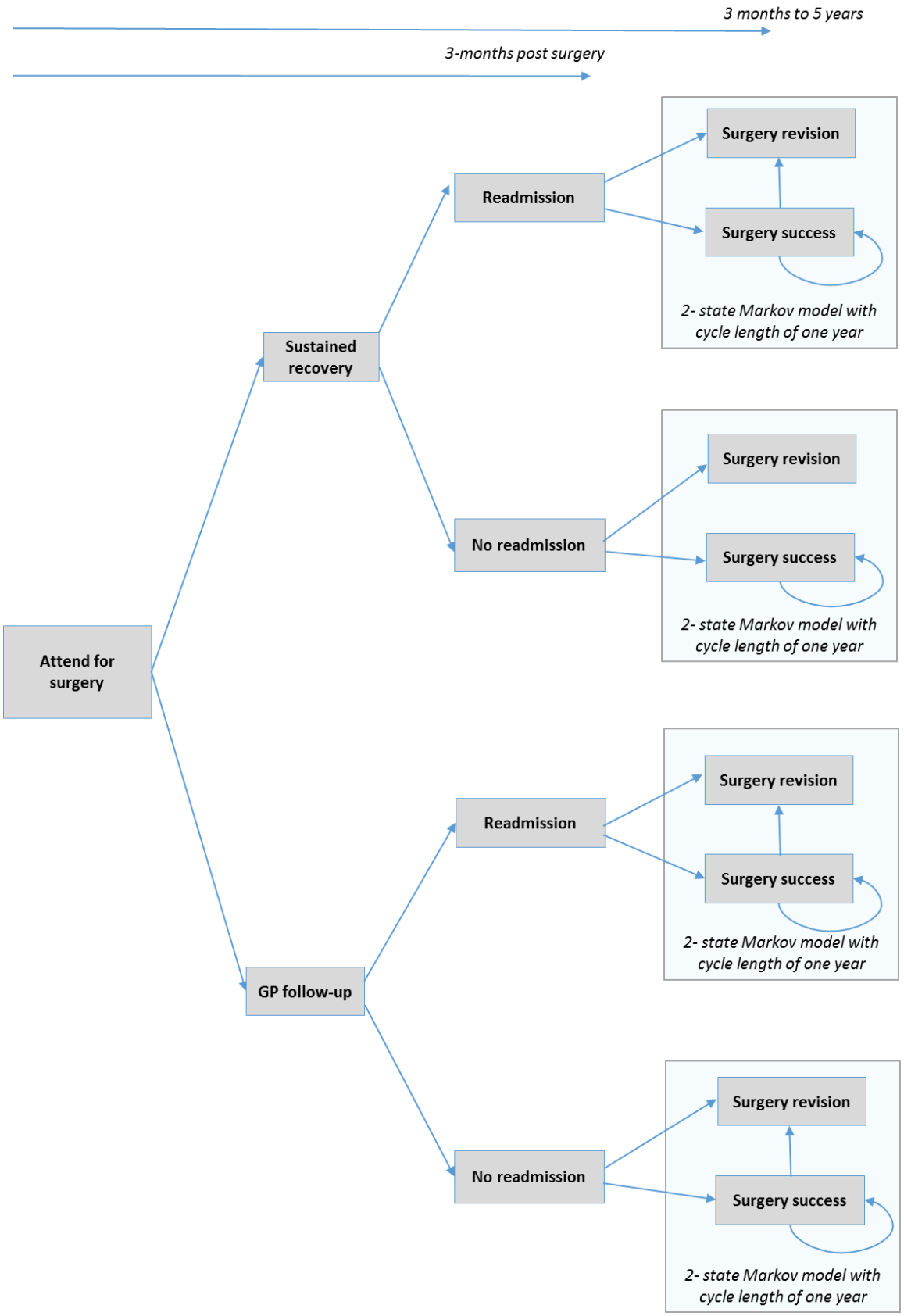
The company noted training costs were excluded from the model as training is provided by Entellus.

The following costs were included: cost of initial surgery for each treatment option, cost of GP visits, cost of readmission, cost of pain management and cost of revision surgery. The proportion of patients experiencing each of these complications differed by treatment type. All input parameters used within the model are described in full in subsequent sections.

The company utilised data from the key clinical study, the REMODEL trial [4] (described fully in Section 3) and a national audit published in 2003 [15]. The national audit comprises data on surgery for nasal polyposis and CRS in 87

hospitals in England and Wales during a 6-month period in 2000. Patients (n=3,128) undergoing surgery were prospectively enrolled within the audit and results at follow-up 3 and 12 months post operatively were reported in the initial publication [15]. Longer term outcomes were reported in 2 further publications [17, 72]. The inclusion criteria were broad meaning that a wide spectrum of patients was included. Outcomes were reported for patients with and without polyps separately, with the company making use of the without polyp data within its model.

Figure 4.2: Model structure



4.2.4 Critique of model structure

The EAC critically appraised this model using the methodology of Drummond and Jefferson (1996) [73]. The appraisal checklist is reported in Appendix 5. This checklist highlighted that the cost year within the model was not consistent and that older costs had not been inflated. This oversight is likely to have a very limited impact upon the results of the model.

The EAC independently replicated the company's calculations employed in the model in order to confirm their accuracy. No errors were identified during the generation of the base case results. The EAC also independently replicated the company's tornado diagram noting that some inputs were omitted from the company's diagram, despite being key drivers, for example the unit cost of the procedure with FESS. Furthermore, the results in the tornado diagram for the monthly rate of GP visits beyond 3 months with FESS did not vary intuitively and could not be replicated by the EAC.

The time horizon of the model in its base case was 5 years to allow all short and medium term costs to be included. Justification for this time horizon was that national audit data were available for 5 years post-surgery for patients having FESS. Data on XprESS MSDS were extrapolated up to 5 years. Other published clinical UK data (n = 1,459) suggest that repeated hospital visits for CRS may occur over a longer time frame (mean of 12.9 years) [23]. Therefore in order to capture all material differences between FESS and XprESS MSDS a longer time horizon may be required. However, the EAC acknowledges that the uncertainty introduced by modelling a longer time frame would be materially higher, potentially undermining the analyses. Hence, pragmatically the EAC judged that this time horizon was appropriate and allowed key differences between FESS and XprESS to be captured. Some assumptions were made in order to extrapolate data for XprESS MSDS and the EAC sought advice from clinical experts around these assumptions.

The company utilised the risk of nasal bleeding at discharge from hospital to determine the risk of GP visits and hospital readmissions in the 3 months following surgery. Expert advice around GP visits post-surgery was mixed. Three of 4 experts judged that there would be no difference in GP visits for FESS and XprESS MSDS patients. However, the 4th thought fewer GP visits would be required with balloon dilation. In addition, 2 of the 4 experts thought nasal bleeding at discharge was a good indicator of an increased likelihood of GP visits, whilst the remaining 2 did not. The advice relating to nasal bleeding being an indicator for hospital readmission was similar: 2 of the 4 experts judged that it is a good indicator whilst the remaining 2 thought that readmission with bleeding were very uncommon within the first 3 months post-surgery. Based on the conflicting of expert advice received it appears

that it was plausible for the company to build these assumptions into the model structure and to at least explore the impact cost implications, ideally using several scenarios.

Revision surgery was modelled at different rates in the first 12 months following surgery and the following 4 years. The revision rate in the first 12 months following surgery was taken from the REMODEL trial directly - 1.4% for XprESS MSDS versus 1.6% for FESS (erroneously extracted from trial) [4]. Revision surgery in the 4 years following the year of surgery was modelled using data from the REMODEL study over 12 months combined with data from the national audit [4, 15]. Within the company's model a greater proportion of FESS patients underwent revision surgery during these 4 years than XprESS patients (2.9% versus 2.5% per year). When asked about the likelihood of revision surgery with either treatment, 2 experts expected there to be no difference (or that any difference had yet to be determined) and the remaining 2 expected revision rates to be higher for patients having balloon dilation. Expert advice was also mixed regarding the rate of revision surgery at 12 months being an indicator for revision surgery over 5 years with 2 experts stating that link could not be made and a third stating that it could be made. The final expert finds that very few patients require revision surgery within 12 months of FESS. This is consistent with evidence from the REMODEL study whereby 1 patient in each arm underwent revision surgery within the first 12 months [4]. Given the experts input surrounding the difference in revision rates by treatment type and the low numbers of patients requiring revision surgery in the REMODEL study, the EAC judges that the inclusion of a difference between FESS and XprESS MSDS in the longer term is not sufficiently supported by the currently available evidence for inclusion in the base case of the model. This is discussed further in Section 4.2.5.

The cost of training surgeons was excluded from the model. Justification for this was provided by the company in that the training is provided free of charge by Entellus. There would, however, be an opportunity cost of the surgeon's time for attending the course. This cost has been discussed further by the EAC in Section 4.2.7.

In addition, the cost of pain medication following revision surgery was omitted from the model. This cost was extremely low and only a proportion of patients require revision surgery, hence the impact of this on the results of the model will be negligible.

Discounting was applied within the model for those costs incurred in future years. The EAC noted a minor error in the company's discounting calculations for revisions including those under local anaesthetic. This error has been

corrected within the EAC's results reported in Section 4.5, but did not impact upon the company's base case result.

In Section 9.1.6, the company listed 6 assumptions that had been made during the development of the model. These are replicated below:

- "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 3 months post-discharge patients could have a sustained recovery or require 1 or more GP visits. This is aligned with the findings of the national audit [15].
- 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 1 of 2 mutually exclusive Markov health states, where they have a surgery revision or sustain recovery. Surgery revision is an absorbent health state as it is assumed that patients can only have 1 revision surgery. This is because the number of patients expected to have more than 1 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 national 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."

The EAC has identified the following additional assumptions made by the company relating to the model structure:

- The risk of revision surgery up to 18 months following initial surgery predicts the risk of revision surgery up to 5 years following initial surgery. The plausibility of this assumption is described in full in Section 4.2.5 and explored in Section 4.5.

- Nasal bleeding at discharge from hospital is a predictor of GP visits and readmission to hospital in the first 3 months following surgery. Clinical experts have advised that this assumption may be plausible as described in Section 4.2.5.

- The risk of revision surgery and GP visits in years 2-5 is independent of the risk of GP visits and readmission in the first year, i.e. patients who have GP visits or readmissions to hospital are not at lower or higher risk of revision surgery in years 2-5 than those who do not visit the GP or have a readmission. This simplifying assumption will have a limited impact on the result of the model.

- Patients requiring revision surgery are assumed to have this using the same procedure with which their initial surgery was carried out. This simplifying assumption will have a limited impact on the result of the model.

- Outcomes excluded from the model include device related adverse events (although the company notes these will be captured through GP visits and readmission), number of post-operative debridements, changes in ostial patency and patient-reported tolerance of procedure. These were assumed to be equal across both treatment arms. This simplifying assumption will have a limited impact on the result of the model.

4.2.5 Clinical parameters and variables

The company identified its model inputs from 2 key sources: the clinical evidence review, specifically the REMODEL study [4] and a national audit published in 2003 [15] as described in Section 4.2.3.

The EAC validated the input parameters used by the company via 2 methods. First, advice was sought from the clinical experts assigned by NICE (correspondence log, appendix 1, collated responses, pages 5 and 19-21). Second, a targeted literature searching was undertaken to identify any relevant published literature. Each clinical input has been described and critiqued by the EAC and an overview provided in Table 4.3. Where discrepancies existed between the company's model and submission document, the input used within the model has been reported.

Table 4.3: Clinical parameters used to populate company's model

Variable	Value	Source	EAC comment
Readmission within 90 days of surgery: FESS	4.10%	National audit [15]	The base case value used by the company is consistent with the audit data.
Readmission within 90 days of surgery: XprESS MSDS	2.30%	National audit data combined with relative risk of nasal bleed from REMODEL [4, 15]	The base case value used by the company is consistent with the data sources utilised.
Revision surgery up to 12 months: FESS	4.1%	National audit [15]	This value has been incorrectly extracted by the company and should be 4.7%.
Revision surgery up to 12 months: XprESS MSDS	3.6%	National audit data combined with relative risk of revision surgery from REMODEL [4, 15]	There is an error in the calculation of this value, due to an error in the relative risk of revision calculation. The value should be 3.87%.
Revision surgery between 12 months and 5 years: FESS	2.9%	National audit data [15]	Due to the incorrect extraction of the company for the first year, this value has been calculated incorrectly and should be 2.7%.
Revision surgery between 12 months and 5 years: XprESS MSDS	2.5%	National audit data combined with relative risk of revision surgery from REMODEL [4, 15]	There is an error in the calculation of this value, due to an error in the relative risk of revision calculation. The value should be 2.35%.
Percentage requiring GP visits within 3 months of surgery: FESS	42%	National audit data [15]	The base case value used by the company is consistent with the audit data.
Percentage requiring GP visits within 3 months of surgery: XprESS MSDS	24%	National audit with relative risk for nasal bleed applied from REMODEL [4, 15]	The base case value used by the company is consistent with the data specified.
Rate of GP visits in first 3 months	1.861	National audit data [15]	The base case value used by the company is consistent with the audit data.

Monthly rate of GP visits in 3 months to 5 years following surgery: FESS	0.12	National audit data [15]	The base case value used by the company is consistent with the audit data.
Month rate of GP visits in 3 months to 5 years following surgery: XprESS MSDS	0.1	National audit data with percentage difference in CRS event from REMODEL applied [4, 15]	The base case value used by the company is consistent with the data specified.
Proportion under local anaesthetic: FESS	0% in base case; 2% in scenario analysis	Expert advice	The values used by the company appear to be consistent with the advice they received.
Proportion under local anaesthetic: XprESS MSDS	0% in base case; 60% in scenario analysis	Expert advice	The values used by the company appear to be consistent with the advice they received.

Readmission within 90 days of surgery: FESS

The rate of readmission to hospital within 90 days of surgery for FESS was taken from the national audit published in 2003 [15]: 4.1% of patients having sinus surgery only (with no polyp removal) had a sino-nasal readmission within 3 months of their surgery. HES data were not available within the public domain to validate this data. The Royal College of Surgeons quality dashboard provides data on readmissions by CCG, but at 7 and 30 days only [74]. However, experts advised that the data from the 2003 audit will be largely applicable today with the exception of the number of cases undertaken as day cases. The national audit data comprises a wider population of patients than those eligible for surgery with XprESS MSDS. However, no alternative data more specific to the population eligible for surgery with XprESS MSDS were available, hence this value represents the best available data.

Readmission within 90 days of surgery: XprESS MSDS

The company determined the rate of readmission in the 3 months post-surgery with XprESS MSDS by applying a relative risk of nasal bleeding to the risk of readmission with FESS. The relative risk of nasal bleeding was

calculated as 0.57 as 32% of XprESS MSDS patients and 56% of FESS patients had nasal bleeding at discharge [4]. As described in Section 4.2.4, the experts were divided in whether nasal bleeding post-surgery would be an appropriate indicator of readmission. However, as a number of experts agreed with the company's approach the EAC judges the values used by the company to be plausible in the base case.

Revision surgery up to 12 months: FESS

The rate of revision surgery up to 12 months following surgery was taken from the national audit data and reported by the company to be 4.1%. The EAC could not verify this number but instead found the that patients having non-polyp procedures had a rate of revision of 4.7% [15]. Alternative sources were considered for more recent data on revision surgery (HES data were not available within the public domain):

- Philpott *et al.* (2015) reported on revision surgery in a recent cross-sectional cohort study based on data from self-reported patient questionnaires. Within this study, 13% (21/106) of patients without nasal polyps reported having repeated sinonasal surgery. The recurrence time (time from initial surgery to a hospital visit where the questionnaire was completed) occurred at a mean of 12.9 years and a median of 8 years [23]. From this data it is not possible to determine the revision rate at 12 months or 5 years post-surgery. However, given that patients included in the study had their primary surgery 12.9 years ago and 13% of participants had revision surgery, assuming a linear relationship, one could expect the annual rate of revision surgery to be around 1% per year.

- Hopkins *et al.* (2009) reported long-term outcomes from the national audit first published in 2003 [15, 72]. Within this paper, revision surgery rates over time were reported for non-polyp patients. These showed that at 12 months around 2% of patients had undergone revision surgery, at 36 months, around 13% and at 5 years 15.5% [72].

- The Royal College of Surgeons quality dashboard provides data on reoperations by CCG, but at 30 days only [74].

- The REMODEL trial reports on revision rates for the FESS arm at 12 months, finding that 1.7% (1/59) (95%CI: 0.04% - 9.09%) of patients had revision surgery within 12 months and 6.9% (2/29) (95%CI: 0.85% - 22.77%) at 18 months [4]. Deriving revision rates from very rare events is subject to great uncertainty, hence the confidence interval around

these revision rates (estimated by the EAC, rather than reported in the paper) are wide.

The EAC judges that the value from the REMODEL trial represents the most applicable data, given that this is relevant to the patient population eligible for surgery with XprESS MSDS [4]. This, lower revision rate, also appears to be more consistent with the more recent data from Philpott *et al.* (2015) assuming that the assumption of linearity of revision surgery holds [23].

Revision surgery up to 12 months: XprESS

The rate of revision surgery with XprESS MSDS was derived by applying the relative risk of revision surgery from the REMODEL study to the baseline risk of revision surgery from the national audit [15, 75]. The EAC attempted to replicate the company's calculations in deriving the rate of revision surgery for XprESS MSDS, but could not do so. The EAC found the rate of revision at 12 months in the REMODEL trial to be 1.7% (95%CI: 0.03% - 7.30%) for the FESS arm and 1.4% (95%CI: 0.04% - 9.09%) for the XprESS MSDS arm. These values were not significantly different and represented 1 patient in either arm requiring revision surgery [4]. The relative risk of revision surgery can be calculated as 0.82 and when applied to the risk of revision surgery from the national audit data gives a risk of revision of 3.87%.

However, given that only 1 patient in each arm required revision surgery, the EAC sought expert opinion on whether the rate of revision would vary between patients having surgery with XprESS MSDS and those having surgery with FESS. As explained in Section 4.2.4, none of the experts advised that the rate of revision surgery would be lower with XprESS MSDS than FESS and 2 experts expected the rate to be higher with balloon dilation. As such, the EAC judges that the evidence and advice does not support any significant difference in revision rate at 12 months. The EAC therefore suggests that the rate of revision surgery from REMODEL is used within the base case model, rather than this value adjusted for a higher baseline revision rate [4].

Revision surgery between 12 months and 5 years: FESS

The rate of revision surgery between 12 months and 5 years post-surgery has been calculated using longer term follow-up data from the national audit data. This data shows that at 5 years, non-polyp patients had risk of revision surgery of 15.5% [72]. The company subtracted from this their risk of revision surgery in the first year (4.1%) and divided the remainder by 4 to derive a rate of 2.85% per year. There a number of issues with this method. First, as mentioned previously, the proportion of patients undergoing revision surgery

in the first year should be 4.7% rather than 4.1%. Second, the cohort of patients included in the longer term follow-up data have a lower rate of revision surgery in the first year around 2% versus 4.7%, hence the rate of revision surgery in subsequent years in the company's model may be understated[15, 72]. This data is, however, based on surgery occurring 16 years ago.

More recent data sources are provided under "revision surgery up to 12 months: FESS". From these the most recent analysis is that by Philpott *et al.* (2016) [23]. From this study, an annual revision rate of 1% can be crudely estimated [23].

Expert advice has indicated that there is either no evidence to support a difference in revision rates over time with either FESS or XprESS MSDS or that the revision rate would be higher with XprESS MSDS. Therefore, the EAC judges that there is not sufficient evidence to model a difference in revision surgery between arms in the 12 month to 5 years following surgery. Therefore, the EAC deems that the using an annual rate of revision of 1% in both arms from Philpott *et al.* (2016) [23] would be more appropriate. This value is similar to the low rates reported in the REMODEL trial (between 1-2% in first year, based on the mean value reported, noting that confidence intervals around these values are wide) [4].This value is likely to err on the side of caution as the cost of revision surgery is equal to the cost of initial surgery and therefore differs by arm. Hence if the magnitude of revision surgery is lower, this cost difference will be lower.

Revision surgery between 12 months and 5 years: XprESS MSDS

The risk of revision surgery between 12 months and 5 years for patients having surgery with XprESS was derived again by applying a relative risk from the REMODEL study to the national audit data for FESS [4, 15, 72]. The relative risk used was identical to that for revision surgery up to 12 months which was incorrectly calculated. In addition it is reported there was no significant difference in revision rates for the FESS and XprESS MSDS arms at either 12 or 18 months [4]. At 12 months 1 patient in each arm required revision surgery and of those patients followed to 18 months, 1 XprESS MSDS patient (2.7%, 95%CI: 0.07% - 14.1%) and 2 FESS (6.9%, 95%CI: 0.8% - 22.8%) patients required revision surgery [4]. Given that these are rare events, the confidence around these estimates is very wide and hence little can be concluded from such small numbers. As described previously, experts have advised that there is no evidence to support a difference in revision rates between the 2 treatment arms and that any difference in revision rate at 12 months may not mean there is a difference between 12 months and 5 years. Therefore, the EAC judges that a lower rate of revision surgery with XprESS

MSDS cannot be justified and recommends the use of the revision rate for FESS for both treatment arms.

Percentage requiring GP visits within 3 months of surgery: FESS

The proportion of FESS patients requiring a GP visit within 90 days of surgery was taken from the national audit data which reported that 42% of patients undergoing sinus surgery without polyp removal required contact with their GP [15]. This value is appropriate for use within the model given the absence of data more specific to the patients identified by the scope.

Percentage requiring GP visits within 3 months of surgery: XprESS MSDS

The proportion of XprESS patients requiring a GP visit within 90 days of surgery was estimated by the company. The company assumed that nasal bleeding at discharge was a predictor of subsequent GP visits and therefore applied the relative risk of nasal bleeds with XprESS compared to FESS from the REMODEL data to the national audit data reporting on GP visits following FESS [4, 15]. The relative risk for nasal bleeding was correctly calculated at 0.57. When applied to the 42% of FESS patients visiting the GP, the value for XprESS patients was estimated to be 24%.

The EAC verified the company's assumption around nasal bleeding being a predictor of post-surgery GP visits with clinical experts as described in Section 4.2.4. Half of experts agreed with the company, that the relative risk of nasal bleeds was an appropriate indicator of GP visits. The EAC is therefore satisfied with the company's input parameter in the base case, but judges that sensitivity analysis be conducted around this assumption.

Rate of GP visits in first 90 days

The company derived the rate of GP visits in the first 90 days following surgery from the national audit data. For those patients making contact with their GP, an average of 1.861 contacts were made [15]. Experts advised that data taken from the national audit is still relevant today. This value was applied to all arms of the model and is appropriate for use within the model given the absence of data more specific to the patients identified by the scope.

GP visits in 5 years following surgery: FESS

The company derived the monthly rate of GP visits between 90 days and 5 years after surgery from the national audit data [15]. Due to rounding within the published audit data, there was a very minor error in the number

estimated for use in the model. However, this error was only apparent beyond 4 decimal places and hence is negligible. In the 3 months to 5 years following surgery, GP visits occurred at a rate of 0.1178 per month [15]. This corrected value is appropriate given the absence of data more specific to the patients identified by the scope.

GP visits in 5 years following surgery: XprESS MSDS

The monthly rate of GP visits between 90 days and 5 years post-surgery with XprESS was derived through applying the percentage difference in acute exacerbations with FESS and XprESS from REMODEL to the national audit data used for the FESS arm (described above) [4, 15]. The acute exacerbations percentage difference was calculated as shown in Table 4.4.

Table 4.4: Percentage difference in acute exacerbations from REMODEL

	12 months prior to surgery	12 months post-surgery	Difference
XprESS MSDS	5.1	0.9	-4.2
FESS	4.5	0.8	-3.7
Percentage difference			-13.5%

The EAC verified the company's assumption around acute exacerbations over 12 months being a predictor of 5 year post-surgery GP visits. The experts agreed that the number of acute exacerbations is a useful marker for determining the number of GP visits over time and as such the EAC is satisfied with the company's input parameter.

Proportion under local anaesthetic: FESS

The company assumed that in its base case all patients underwent surgery under general anaesthetic. A scenario analysis was conducted whereby a proportion of patients underwent surgery under local anaesthetic in an ambulatory setting. For patients having FESS, 2% were assumed to have local anaesthesia based on UK expert opinion. The EAC sought expert advice on this and all experts specified that very few FESS cases are carried out under local anaesthetic with a range of between 0-5% provided. Therefore, the EAC deems that the company's estimate used in their scenario analysis is valid.

Proportion under local anaesthetic: XprESS MSDS

As with FESS, the company assumed that in its base case all patients underwent surgery with XprESS MSDS under general anaesthetic. A scenario analysis was conducted whereby a proportion of patients underwent surgery under local anaesthetic in an ambulatory setting. For patients having a procedure with XprESS MSDS, 60% were assumed to have local anaesthesia based on UK expert opinion. The majority of expert advice received by the EAC suggested that at present below 10% of balloon dilation procedures are carried out under local anaesthetic, but that this could increase in time up to around 70%. Therefore, the EAC judges the company's scenario analysis to be valid. Within the company's base case, the assumption that all patients underwent surgery under general anaesthetic may be over conservative. The EAC suggests that using a value of 10% may be more appropriate based upon expert advice.

4.2.6 Resource identification, measurement and valuation

The EAC has provided a description and critique of the resource identification, measurement and valuation conducted by the company for use in its *de novo* economic model. This is summarised in Table 4.5. All resource use apart from that reported is assumed to be equal in the XprESS MSDS and FESS arms of the model. Where discrepancies existed between the company's model and submission document, the input used within the model has been reported.

Table 4.5: Resource usage in company's model

Variable	Value	Source	EAC comment
Cost of procedure under general anaesthetic: FESS	£2,594	Comprises the following, details of which are provided in the write up below: procedure duration; cost of theatre, nurse and surgeon; gowns and trays; length of hospital stay and cost of hospital stay.	The EAC has critiqued and redone the bottom-up costing and estimates the cost of the procedure to be £657.
Cost of procedure under general anaesthetic: XprESS MSDS	£984	Comprises the following, details of which are provided in the write up below: procedure duration; cost of theatre, nurse and surgeon; gowns and trays; length of hospital stay and cost of hospital stay.	The EAC has critiqued and redone the bottom-up costing and estimates the cost of the procedure to be £428.
Pain medication: FESS	2.8 days	REMODEL [4]	The base case value used by the company is consistent with the data source specified.
Pain medication: XprESS MSDS	1 day	REMODEL [4]	The base case value used by the company is consistent with the data source specified.
Cost of pain medication	£0.13	British national formulary (BNF): 400mg ibuprofen 3 times per day [76].	The base case value used by the company is consistent with the data source specified.
Cost of GP visit	£94.43	Comprises: Unit cost of 11.2 min GP visit = £45 (PSSRU) [77]; Unit cost of prescription = £23.30 (PSSRU) [77] Steroid nasal spray = £11.01 (BNF) [76] Course of macrolide = £15.12 (BNF) [76]	This cost includes the unit cost of a prescription in additional to drug costs, hence these costs are double counted. The wrong GP cost has been used. Further, expert advice has indicated that other antibiotics would likely be prescribed and patients may not need both a steroid nasal spray and a course of antibiotics. The EAC has generated a cost of between £39 and £50

Variable	Value	Source	EAC comment
			dependent on the treatment required.
Cost of readmission	£601	NHS ref costs (2011/12): Non-elective inpatient (short stay) minor nose procedure (CZ12Y) [78].	This cost has not been inflated to the 2014/15 price year. Once inflated the cost is equal to £623.55. Costs from NHS reference costs 2014/15 would have been most appropriate.
Cost of revision surgery	Equal to original surgery	Assumption	The assumption of costs being equal to the cost of original surgery is appropriate.
Cost of procedure: FESS (local anaesthetic)	£1,636	Used ratio (0.631) from hernia surgery, reported by Zilvetti [79].	A bottom-up costing approach would have been more accurate.
Cost of procedure: XprESS (local anaesthetic)	£620	Used ratio (0.631) from hernia surgery, reported by Zilvetti [79].	A bottom-up costing approach would have been more accurate.

Cost of procedure with FESS – consumables, procedure time, nurse time, surgeon time, length of stay

The company determined the cost of surgery with FESS using a bottom-up costing approach. No business cases could be identified by the EAC through targeted searching or via the clinical experts to fully verify the bottom-up costing; rather each component was verified individually. This included the following components:

- Duration of surgery of 90 minutes. The company sought advice from UK experts on this parameter. Expert advice received by the EAC suggested that FESS in those patients who would be eligible for treatment with XprESS MSDS lasts 40, 45, 90 or 120 minutes. The expert who suggested that the procedure lasts 90 minutes explained that he treats patients at the worse end of the spectrum; hence the surgery may last longer. He also does not use balloon dilation therapy. The EAC contacted the expert who suggested that the procedure takes 120 minutes to confirm that this estimation was in patients who would otherwise be eligible for balloon therapy. He corrected his estimate stating that 120 minutes for FESS was based on his case mix and

therefore more severe patients than those undergoing balloon therapy. He stated that FESS in the patients in scope would not take much longer than balloon therapy (estimate of 30 minutes). Therefore, the average duration of FESS has been estimated as 42.5 minutes. This is based on the average for those surgeons treating patients eligible for balloon therapy (40 and 45 minutes) combined with the information from the third expert stating that the procedure does not take much longer than balloon dilation. Alternate sources suggest that the duration of FESS is lower than the average specified by the experts treating patients eligible for balloon therapy, with the national audit specifying 39.6 minutes for all patients and 41.5 minutes for patients without polyps [15] and a HTA report specifying 46 minutes [16].

- Cost of operating theatre of £20 per minute. The company derived the cost of the operating theatre from the NHS Institute for Innovation and Improvement who approximated the hourly operating cost to be £1,200 [80]. Information services division (ISD) Scotland report more accurate operating theatre costs specific to Scotland. For ENT surgery in 2014/15 the average theatre cost per hour was £819 [81]. This cost is inclusive of general consumables used during surgery and also of staff costs according to information on the ISD Scotland website. The EAC has contacted ISD Scotland to confirm this information, but to date no response has been received.

- Cost of a surgeon of £1.77 per minute. This cost has been correctly extracted from Personal Social Services Research Unit (PSSRU) [77]. Staff costs are already captured within the ISD Scotland theatre cost, but it is unknown whether they are included within the operating theatre costs used by the company.

- Cost of a nurse of £1.47 per minute. This cost has been correctly extracted from PSSRU [77]. The cost of an anaesthetist has not been included within the company's costings. Staff costs are already captured within the ISD Scotland theatre cost, but it is unknown whether they are included within the operating theatre costs used by the company.

- Gowns costing £40 per person. This cost was estimated based upon the list prices of gowns provided online. General consumable costs are already included within the ISD Scotland theatre cost, but it is unknown whether they are included within the operating theatre costs used by the company.

- Tray and camera costing £35 per surgery. The company correctly extracted the tray cost from the NHS Institute for Innovation and

Improvement [80]. General consumable costs are already included within the ISD Scotland theatre cost, but it is unknown whether they are included within the operating theatre costs used by the company.

- Length of stay in hospital of 0.97 days. This was obtained from HES data. However, the full reference was not provided. The EAC has concerns around the use of HES data to populate the model given the likely heterogeneity in patient populations undergoing FESS compared with those undergoing balloon dilation. Given that the company advised that XprESS MSDS is not indicated for patients with severe polypoid disease (correspondence log, page 10) those patients undergoing FESS within the NHS may, on average, have more severe disease than those undergoing balloon dilation. Furthermore, HES does not report length of stay data to a degree of granularity to be used for this purpose. Rather, the length of stay in days for each patient can only be an integer value. Hence a value of 0.97 days reflects that some patients will be day cases with a stay of 0 days and others will remain in hospital overnight. The EAC asked experts how long patients with the same severity of illness would remain in hospital post FESS or a procedure with XprESS MSDS. The reported length of stay under general anaesthetic was similar for the 3 experts who provided information on FESS and balloon dilation. Length of stay estimated following FESS under general anaesthetic ranged from 4 to 8 hours (0.167 to 0.33 days).

- Cost per day in hospital of £400. The company took this value from a Deltex Medical report on the cost of a day in a general or surgical ward (reported to be up to £400) [82]. This estimated cost was reported as part of a press release in 2006. NHS reference costs 2014-15 report the elective inpatient excess bed days to be £359 per day. NHS reference costs 2014-15 report costs for elective inpatient excess bed days for minor sinus procedures (CA29Z), intermediate sinus procedures (CA28Z), major sinus procedures (CA23Z) and complex sinus procedures (CA26Z). Costs range from £334 - £425, with a weighted average cost of £370, similar to the overall cost and similar to the £400 used by the company [83]. Excess bed day costs were used in the absence of other data reporting on the cost of the cost of being in hospital. Using excess bed days costs for this purpose is limited in that any care above and beyond the patient being sat in hospital is not covered and the costs rely on accurate coding of patient resource usage. Input from experts informed the EAC that patients would usually wait in the recovery area adjacent to theatres for a short period and then reside on a day care or short stay ward until they are discharged from hospital (correspondence log, appendix 1, collated responses, page 36).

Based on the critique above, the EAC has conducted additional bottom-up costing as reported in Table 4.6.

Table 4.6: EAC bottom-up costing of FESS under general anaesthetic

Component	Value	Source and explanation
Length of procedure	42.5 minutes	Clinical experts. Average of 2 experts providing advice on *both* FESS and XprESS MSDS (40 and 45 mins) and a third experts stating FESS does not take much longer than 30 minutes.
Cost per minute of theatre	£13.65	ISD Scotland [81] ENT theatre = £819 per hour.
Length of stay in hospital	5 hours (0.208 days)	Clinical experts. Average of 3 experts providing advice on *both* FESS and XprESS MSDS (4 hours, 4-6 hours and 6 hours).
Cost per day in hospital	£370	NHS reference costs 2014-15: elective inpatient excess bed day weighted average of CA26Z, CA27Z, CA28Z and CA29Z [83].
Total cost	**£657**	

Cost of procedure with XprESS – consumables, procedure time, nurse time, surgeon time, length of stay

The company also determined the cost of surgery with XprESS MSDS using a bottom-up costing approach. This included the following components:

- Duration of surgery of 30 minutes. The company sought advice from UK experts on this. Expert advice received by the EAC suggested that XprESS MSDS under general anaesthetic lasts between 20 and 30 minutes.

- Length of hospital stay of 0.43 days. This was obtained from HES data. However, the full reference was not provided. As stated previously due to the heterogeneity of patients and non-granularity of the data, the EAC has concerns around the use of HES data. Experts advised that the length of stay in hospital following balloon dilation therapy would be 3-4, 4-6 or 4 hours (correspondence log, appendix 1, collated responses, pages 26-27). Furthermore, experts advised that those patients in the scope of this decision problem would be treated as day cases.

- All other cost components remained the same as for FESS.

As previously, based on the critique above, the EAC has conducted additional bottom-up costing as reported in Table 4.7.

Table 4.7: EAC bottom-up costing of XprESS MSDS under general anaesthetic

Component	Value	Source and explanation
Length of procedure	26.7 minutes	Clinical experts. Average of 3 experts providing advice on both FESS and XprESS MSDS (20, 30 and 30 mins).
Cost per minute of theatre	£13.65	ISD Scotland [81] ENT theatre = £819 per hour.
Length of stay in hospital	4.17 hours (0.174 days)	Clinical experts. Average of 3 experts providing advice on both FESS and XprESS MSDS (3-4 hours, 4, and 4-6 hours). Experts advised that patients in scope are likely day cases.
Cost per day in hospital	£370	NHS reference costs 2014-15: elective inpatient excess bed day weighted average of CA26Z, CA27Z, CA28Z and CA29Z [83].
Total cost	**£428**	

Pain medication: FESS

The duration of pain medication following surgery was taken directly from the REMODEL study which reported that following FESS patients took prescription pain medication for 2.8 days [4]. The use of this value within the model was appropriate.

Pain medication: XprESS MSDS

The duration of pain medication following surgery was taken directly from the REMODEL study which reported that following surgery with XprESS MSDS patients took prescription pain medication for 1.0 day [4]. The use of this value within the model was appropriate.

Cost of pain medication

The cost of pain medication used within the model was negligible (13 pence per day) and comprised 400mg Ibuprofen 3 times a day. The dosage was supplied to the company by clinical experts and costs extracted correctly from taken from British National Formulary [76].

Cost of GP visit

The company's GP visit cost comprised: the visit to the GP, a prescription charge, steroid nasal spray and macrolide. The company received expert advice around the treatments prescribed during a GP visit. In Table 4.8, a breakdown of the cost of a GP visit is provided together with the EAC's critique of this cost. Expert advice received by the EAC indicated that if a patient presented with a blocked nose due to rhinosinusitis then a steroid spray would be given. If the patient presented with an infection post-operation then antibiotics would be prescribed. The expert advised that most GPs would prescribe amoxicillin or doxycycline, rather than azithromycin, as first line treatment post-operation. This suggests that patients may present to their GP with either a blocked nose or infection and as such would only require the treatment specific to their problem. The national audit paper does not provide specific reasons why patients consulted their general practitioner for sino-nasal problems [15].

Table 4.8: Cost of GP visit

Component	Company cost	EAC comment
GP visit	11.7 min GP visit = £45 sourced from PSSRU [77].	Cost has been extracted incorrectly and should be £37 for a GP visit excluding qualification costs.
Prescription charge	£23.30 sourced from PSSRU [77].	This cost is the net ingredients cost per consultation. As the costs of the drugs themselves are already included below costs are double counted. A dispensing cost of 90p may be included [84].
Steroid nasal spray - Fluticasone propionate	£11.01 sourced from BNF.	Cost has been extracted correctly.
Macrolide - Azithromycin 500 mg once daily for 3 days	£15.12 for capsules sourced from BNF [76].	Cost of £1.74 for tablets, 3-tab pack also provided on BNF. Clinical expert advised that amoxicillin or doxycycline would be prescribed first line. Amoxicillin, 500 mg every 8 hours, £1.57, 500 mg capsules, 21 pack sourced from BNF. Used for 7 days[85]. Doxycycline, 200 mg on first day then 100 mg daily, £1.07, 100 mg capsules, 8-cap pack sourced from BNF. Used for 7 days [86].
Total	**£94.34**	**Blocked nose: £48.91** **Infection: £38.97 to £39.64** **Blocked nose and infection: £50**

Cost of readmission

The company's readmission cost was given as £601 for CZ12V Minor Nose Procedures, 19 years and over with CC sourced from the NHS reference costs 2011/12 for non-elective inpatient (short stay) [78]. There was a minor error in the extraction of this cost, as the EAC found this cost to be £602. The company did not inflate the unit cost, sourced from 2011/12 data to the current cost year which resulted in an underestimation of the unit cost of readmission in the company's submission.

The EAC has recalculated the cost of readmission. The EAC has not included the cost of complications in the unit cost for readmission, rather assuming complications are the reason for the readmission and no further complications occur during the readmission. Hence the EAC judges a day case or non-elective short stay cost is more appropriate. A weighted average of the following costs was calculated:

- Day case - CA24A Minor Nose Procedures, 19 years and over = £971 (1,751 procedures) [83].

- Non elective short stay - CA24A Minor Nose Procedures, 19 years and over = £622 (430 procedures) [83].

The weighted average cost is equal to £902. Within their submission the company is not clear on what would be included during readmission to hospital and as such this cost may be overstated if no procedure is performed.

Cost of revision surgery

The cost of revision surgery was applied as being equal to initial surgery for both FESS and XprESS. One of the 4 experts stated that revision surgery required the same resources as initial surgery whilst the remaining 3 experts suggested that in some cases revision surgery may be longer than initial surgery, but in other cases is shorter. The EAC deems that the company's assumption is on average accurate.

Cost of procedure: FESS (local anaesthetic)

The company calculated a cost ratio between hernia procedures carried out under general or local anaesthetic as reported in the published literature [79]. They then applied this cost ratio (0.631) to the cost of FESS under general anaesthetic to determine the cost of FESS under local anaesthetic (£1,636). The ratio was calculated and applied correctly. Given that this ratio refers to hernia surgery, which may require a different staffing and equipment

complement, the EAC has bottom-up costed FESS under local anaesthetic. This is reported in Table 4.9.

Table 4.9: EAC bottom-up costing of FESS under local anaesthetic (in operating theatre)

Component	Value	Source and explanation
Length of procedure	30 minutes	Clinical experts. Expert providing advice on both FESS and XprESS MSDS and supported by audit data [15, 17] and a HTA report [16].
Cost per minute of theatre	£13.65	ISD Scotland [81] ENT theatre = £819 per hour.
Length of stay in hospital	3 hours (0.125 days)	Clinical experts. Expert providing advice on both FESS and XprESS MSDS (2 -4 hours).
Cost per day in hospital	£370	NHS reference costs 2014-15: elective inpatient excess bed day weighted average of CA26Z, CA27Z, CA28Z and CA29Z [83].
Total cost	**£456**	

Cost of procedure: XprESS MSDS (local anaesthetic)

As with FESS, the company used the cost ratio based on hernia surgery to determine the cost of treatment with XprESS MSDS under local anaesthetic. The ratio was calculated and applied correctly and a cost of £620 determined. Again, the EAC has bottom-up costed the procedure with XprESS MSDS under local anaesthetic. This is reported in Table 4.10.

Table 4.10: EAC bottom-up costing of XprESS MSDS under local anaesthetic (in operating theatre)

Component	Value	Source and explanation
Length of procedure	31.7 minutes	Clinical experts. Average of 3 experts providing advice on both FESS and XprESS MSDS (20, 30 and 45 mins).
Cost per minute of theatre	£13.65	ISD Scotland [81] ENT theatre = £819 per hour.
Length of stay in hospital	2.17 hours (0.09 days).	Clinical experts. Average of 2 experts providing advice on both FESS and XprESS MSDS (3, 2 and 1-2 hours).
Cost per day in hospital	£359.13	NHS reference costs 2014-15: elective inpatient excess bed day[83].
Total cost	**£466***	
* This cost is higher than that for general anesthetic due to a longer procedure time stated from 2 of 3 experts. The cost per minute of a theatre is the same as that used for general anesthetic and may be too high. This uncertainty will be explored within the EAC's sensitivity analyses.		

4.2.7 Technology and comparators' costs

The cost of the consumable used for FESS and XprESS MSDS are shown in Table 4.11.

Table 4.11: Costs used in company's model

Variable	Value	Source	EAC comment
Cost of consumables: XprESS MSDS	£900	Entellus market data	The EAC cannot externally validate the cost of XprESS, but assumes that this is correct. The training cost has been omitted (EAC estimates this to be £5.15 per patient, see following section).
Cost of consumables: FESS	£300	Entellus market data	The EAC attempted to validate this cost through NHS supply chain and contacting Medtronic. However, no data was identified hence the company's cost is assumed to be accurate.

Cost of XprESS

The cost of XprESS MSDS (£900) was provided by the company and cannot be verified on NHS supply chain given that the device is not listed.

The cost of training on the device was not included by the company as training is provided free of charge by the company. However, there exists a time cost to surgeons and other staff relating to training that has been omitted. The company advised that training of surgeons involves a 1 day training course. Other staff members are trained on site using a head model bought in by the company to fit around patient care. The EAC judges that the cost of surgeon time for attending the one-day training course should be included within the analysis. The course is assumed to last 7 hour and hence at a cost per hour of £106[77], costs £742 per surgeon.

Two experts using XprESS MSDS advised that they carry out an average of 4 and 0.5 procedures per month. Assuming that this remains constant over time and the training is valid for 5 years, the cost per procedure is £5.50.

Cost of FESS consumables

The company used a cost of £300 for FESS consumables including blades and burrs. There was limited information provided in the submission regarding these costs, hence the EAC asked the company for more information. The company provided the following information (correspondence log, page 20):

“The average disposable cost of the blade and burr were obtained from several theatre staff members at the hospitals and the brands sourced were Medtronic and Storz.

No capital costs for equipment were included as all other capital equipment used is expected to be standard surgical equipment already available in the surgery suite. Therefore, we excluded the cost of the capital equipment of the microdebrider and only compared the average cost of the consumable/ disposable equipment used in either a FESS (blade/burr) or XprESS (device/system) procedure.”

The EAC confirmed the brand of blades and burrs with experts, 2 of whom reported using Medtronic and the 3rd reported using Gyrus system, but stated that Medtronic is used elsewhere. The EAC searched NHS supply chain for costs relating to these consumables. However, they could not be identified. Therefore, the EAC contacted the supplies department at the Newcastle upon Tyne Hospitals NHS Foundation Trust in order to validate the company’s cost. The supplies department confirmed that a microdebrider had not been purchased since 1999 (correspondence log, page 21); hence the company

has correctly excluded this cost given that it is already available as standard and not replaced regularly. Furthermore, the supplies department confirmed that the blades and burrs are not available on NHS supply chain. The supplies department contacted Medtronic to confirm the cost of blades and burs. To date, no response has been received and hence, in the absence of information to the contrary, the company's cost is assumed to be accurate.

4.2.8 Sensitivity analyses

The company undertook extensive DSA to assess the impact of parameter uncertainty on the results of the model.

First, univariate sensitivity analysis was conducted around all model input parameters. This involved varying each parameter to make it 20% higher and 20% lower. The results of this analysis were presented as a tornado diagram based upon the change in net budget impact per patient. This analysis was useful in identifying the key drivers of the analyses. However, it was limited in that all inputs were varied by the same proportion regardless of how much uncertainty existed for each input parameter. Ideally, a plausible range for each input parameter would have been identified and each input varied within that range. In addition, the tornado diagram reported the change in net budget impact per patient. This meant that where an input was varied, the impact of that variation on the net budget impact, or cost saving, was reported. The EAC judges that presenting the results by cost savings per patient directly would have been more easily interpreted as any occasion where the XprESS MSDS became cost incurring would have been easily identifiable. Within the EAC's additional work reported in Section 4.5 a revised tornado diagram has been generated.

In addition to the univariate analyses, the company undertook multi-way DSA whereby multiple parameters were varied simultaneously. These analyses tested a number of assumptions used to populate the model and are reported in full in Sections 4.3.2 and 4.3.3.

Finally, the company performed threshold analyses around the length of surgery with both XprESS MSDS and FESS. These break even analyses are a useful tool for identifying the cut-off point at which XprESS MSDS is no longer cost saving.

No probabilistic sensitivity analysis (PSA) was carried out by the company and no reason for this omission provided. As a number of the inputs were identified through eliciting expert opinion, rather from the published literature, confidence around inputs may have been unknown and hence PSA omitted. However, PSA would have been useful for assessing the impact of the joint parameter uncertainty within the model. Further, modelling the probability of

revision surgery from the REMODEL study did not report statistically significant cost differences between FESS and XprESS MSDS. As such, within the company's analyses the non-significant difference in revision surgery is assumed to be real. Conducting PSA would have mitigated against this assumption as the analysis allows this uncertainty in significance to be captured.

The company did not perform any analyses to test the structural uncertainty within the model with the exception of varying the time horizon of the model. The EAC judges that it would have been appropriate to run the model assuming that there was no difference in GP visits and readmission in the first 3 months following surgery given that it was assumed that nasal bleeding at discharge was an indicator of each of these things. Some of the expert advice received by the EAC suggests that this assumption may not be valid.

4.3 *Results of de novo cost analysis*

4.3.1 Base-case analysis results

Results from the company's economic model were provided in Section 9.5 of the submission. The EAC replicated the model calculations to verify the results reported. The EAC obtained the same results to those reported within the company's submission. Results from the company's base case model are reported in Table 4.12. These show that XprESS generates cost savings of £1302 per patient over a 5 year time horizon.

Table 4.12: Company's base case results

	XprESS MSDS	FESS	Cost saving per patient
Surgery excluding. equipment	£984	£2,594	£1610
Equipment	£900	£300	-£600
GP visits 3 <months	£42	£74	£32
Pain Management	£0	£0	£0
Admission 3 <months	£14	£25	£11
GP visits beyond 3 months	£511	£590	£80
Revisions	£228	£397	£169
Total	£2,679	£3,981	£1,302

4.3.2 Sensitivity analysis results

The company undertook DSA, multiple scenario analyses and a breakeven analysis. The company addressed the uncertainty around the time horizon of the model by reporting the results over a 1,2,3,4 and 5 year time horizon. The company's results are shown in Table 4.13; these could be replicated correctly by the EAC.

Table 4.13: Company's sensitivity around model time horizon

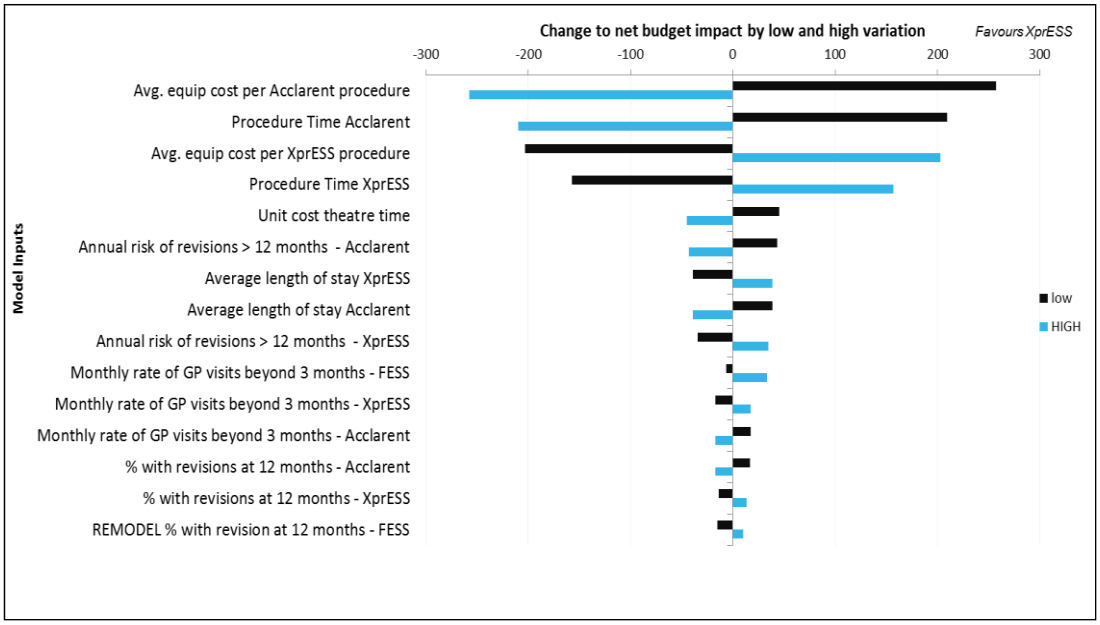
Time Horizon	Cost saving per patient
1 year	£1,117
2 year	£1,167
3 year	£1,215
4 year	£1,259
5 year (Base case time horizon)	£1,302

The company conducted univariate DSA by varying each of the model inputs independently by ±20% and re-calculating the net difference in cost per patient. The company's DSA results were presented in a tornado diagram, Figure 4.3, and summarised in Table 4.14 as the range of cost-savings reported in the DSA. The tornado diagram shown in Figure 4.3 from the company's model has incorrect labelling (Acclarent rather than FESS). The company reported that the main drivers for the results comparing XprESS to FESS include: procedure time; cost of the equipment; length of hospital stay and cost of theatre time. The EAC independently recreated the tornado diagram and agreed with the company's identified key drivers. The EAC did identify an error in the tornado diagram relating to the analysis around the monthly rate of GP visits after 3 months. However, this did not impact on the interpretation of results or the conclusions drawn.

Table 4.14: Company's range of cost saving per patient with XprESS MSDS

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

Figure 4.3: Company's tornado diagram



The company conducted multi-way scenario-based to consider different scenarios and alternative assumptions. The results of the company's multi-way scenario-based sensitivity analysis are shown in Table 4.15, presented as the cost-saving per patient with XprESS compared to FESS.

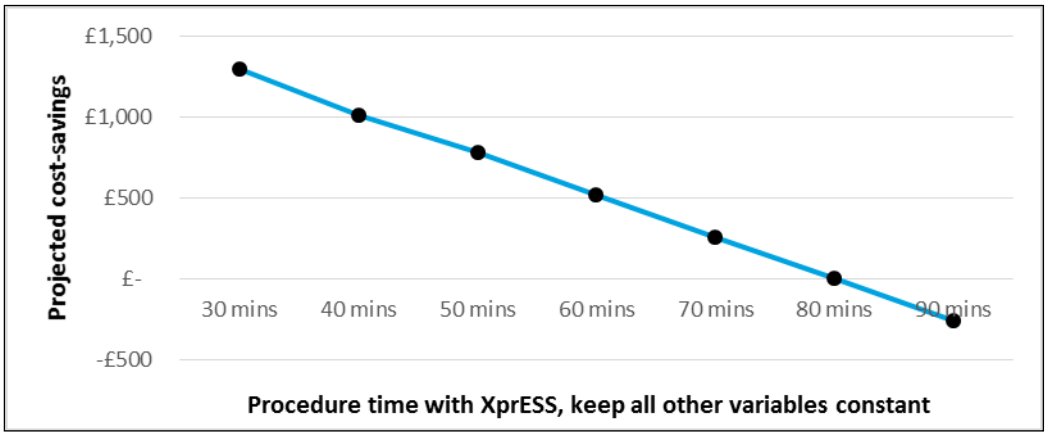
Table 4.15: Company's scenario analyses

Scenario	Base case	Option	Cost saving per patient
Base case	All defaults	NA	£1,302
Anaesthesia	General only	Include local	£1,520
Outcomes Adjustment	UK Adjustment	REMODEL unadjusted	£1,222
Source of estimate - procedure time	UK Experts	Italian RCT	£550
Source of estimate - length of hospital stay	E148 frontal sinus	E133 Intra. Antro.	£1,205
Source of estimate - % under local anaesthesia	UK expert opinion	USA data	£1,302
Unit cost theatre time (per min)	Average surgery	Low cost surgery	£367

The company conducted breakeven analysis by varying the procedure time with XprESS while keeping all other inputs constant. The company reported

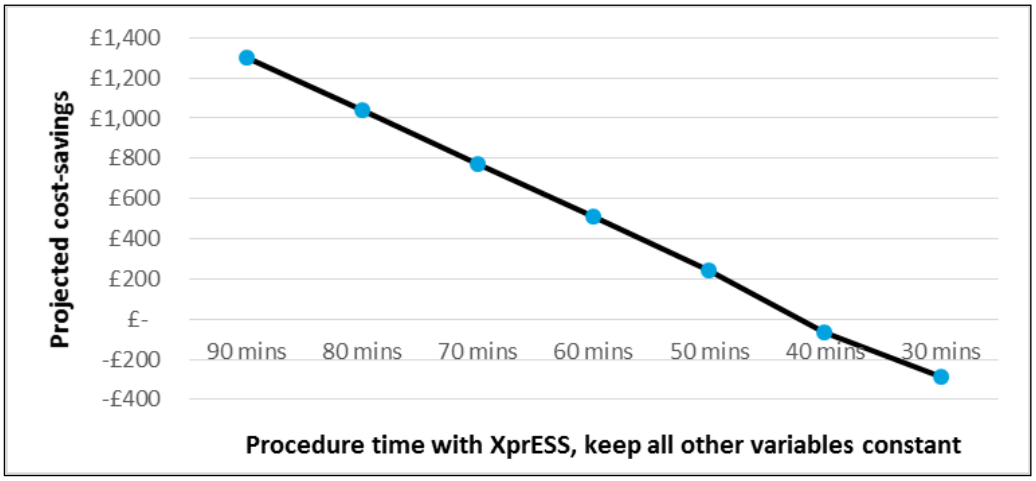
that XprESS was cost-neutral with a procedure time of 80 minutes as shown in Figure 4.4.

Figure 4.4: Company's breakeven analysis varying XprESS MSDS procedure time



The company conducted further breakeven analysis by varying the procedure time with FESS. The company reported that XprESS is cost-neutral or cost-saving when the procedure time with FESS is above 41 minutes, shown in Figure 4.5. The company had a typing error in the title of the horizontal axis on the graph where XprESS should read FESS.

Figure 4.5: Company's breakeven analysis varying FESS procedure time



4.3.3 Subgroup analysis

The scope outlined that the following subgroups should be considered:

- Patients with uncomplicated CRS (or uncomplicated recurrent acute rhinosinusitis).
- Patients with CRS (or recurrent acute rhinosinusitis) with orbital or intracranial involvement.
- Patients with CRS (or recurrent acute rhinosinusitis) with and without nasal polyps.
- Patients with CRS (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 subgroup analysis was carried out by the company. The company reported that the clinical and economic benefits of XprESS relative to both comparators are relevant for all subgroups. The company states that there may be differences in procedure times and length of stay across subgroups, but the relative differences between XprESS and its comparators was expected to be constant. The company reports that the findings of the analysis are assumed to be relevant to all subgroups where XprESS has an indication. The EAC agrees that given the paucity of data, conducting subgroup analysis for each of the specified groups would have been difficult.

4.3.4 Model validation

The company reported that its economic model had been internally validated by calculating the cost in the first year in 2 ways: i) on a decision tree, ii) by cost type in a breakdown of cost type. The company reported that the model calculations were calculated by a primary health economist and cross checked and internally validated by a second modeller. The EAC identified no calculation errors within the base case of the model. A minor error in the discounting calculation cell links was identified when XprESS MSDS procedures under local anaesthetic were included.

The company reported that the results could not be externally validated as no prior models relating to XprESS MSDS were identified in the systematic literature review.

4.4 *Interpretation of economic evidence*

4.4.1 Consistency with published economic literature

In Section 9.8.1 of the company's submission the results of the company's analysis are compared with 1 of the published cost-effectiveness analyses included within the company's review. To recap, these analyses did not consider XprESS MSDS, but other balloon dilation systems, specifically the Acclarent device. The company concluded that its findings were consistent with those published previously by Holy *et al.* (2013) [67]. The EAC agrees with the company's interpretation of its *de novo* model in relation to the study by Holy *et al.* (2013) [67]. As reported in Section 4.1, the EAC identified no studies reporting on the cost-effects of XprESS MSDS versus FESS or other balloon dilations systems used within the NHS. Therefore, it is impossible to make comparisons between the company's *de novo* model and the published literature.

4.4.2 Relevance to NHS settings

The company briefly stated in Section 9.8.2 of the submission that the cost analysis is relevant to all groups of patients and NHS settings in England that are indicated for the use of XprESS MSDS. The EAC judges that the clinical data identified in Section 3 is all based in the US and therefore not directly applicable to the NHS. Clinical data from the pivotal REMODEL study have been utilised within the economic model and whilst this data may not be fully applicable to the NHS, the company has attempted to mitigate against this through considering national audit data and seeking UK expert advice [4, 15]. Whilst using national audit data attempts to generalise the REMODEL data, it also assumes that the REMODEL data is applicable to the wider group of patients included within the audit [4, 15]. All cost data used within the model is specific to the UK NHS. Given the lack of UK clinical data, the company's analyses (including the extensive sensitivity analysis) reflects NHS settings as well as possible.

4.4.3 Strengths and weaknesses of submission

In Section 9.8.3 of the economic submission (strengths and weakness of the analysis), the company identified that the strengths of their analysis were the model structure allowing short and medium term costs to be captured and that all inputs were selected from a UK NHS perspective. Further the company identified that the model's flexibility facilitated consideration of alternative sources of evidence. The company also correctly highlighted 2 key limitations of the analysis: the limited evidence relating to procedure times (a key driver of the analysis) and uncertainty regarding patients outcomes after 2 years

post-surgery. The EAC's judgement of the strengths and weaknesses of the submission is now described.

Strengths of submission

The EAC considered that the analysis matched the scope well. The population included within the model comprised those patients undergoing surgery for CRS in whom all medical therapy had failed. XprESS MSDS was compared with 1 of the comparators listed in the scope (FESS) and the company attempted to make a comparison to other balloon dilation systems used within the NHS by making a comparison to a balloon dilation system previously used within the NHS (Acclarent). The company applied health care system outcomes within the model as specified by the scope. These included length of hospital stay, procedure time, rate of revision surgery, number of sinus-related follow-up appointments, rate of readmission and numbers and grade of staff required. All other outcomes were appropriately assumed to be consistent between the 2 treatment options.

The model structure, a decision tree followed by a Markov model, using an NHS perspective was appropriate for the decision problem. It captured the main differences in resource usage between the treatment options and the reported cost differences. The 5 year time horizon of the model allowed the long term follow-up data from the national audit [15] to be utilised without extrapolating the follow-up data on XprESS too much [4]. As such it is judged that the key cost differences between the technologies will be captured, but that longer term revision surgery and health care utilisation omitted. The company adopted an NHS perspective which was appropriate given that with the model structure used, no differences in personal social services (PSS) resources would have occurred. Discounting was applied within the model to those costs incurred in the future.

Clinical evidence were taken from the REMODEL study, which represents the best available clinical data on XprESS MSDS [4]. Relative risks of clinical events were calculated from this study and applied to national audit data to generate results more specific to the NHS [15]. Additional analyses were conducted using the data from the REMODEL trial directly [4]. Resource use and unit costs were in general appropriate. Where published evidence was scarce, the company sought verification of model inputs with clinical experts, in particular on the length of surgery.

The company conducted extensive DSA to explore the impact of parameter uncertainty within the model. This comprised increasing and decreasing each input by 20%; considering alternative scenarios and conducting a break even analysis on those inputs deemed to be key drivers. The company also

addressed the structural uncertainty of the model somewhat through consideration of different model time horizons.

Weaknesses of submission

The EAC considered there to be a number of weaknesses with the company's submission, some of which have a material impact on the results of the model. The key weaknesses with the model's input parameters are described below and were identified through the critique provided in Section 4.2.5. A full critique of each input parameter along with the EAC's best estimate for each input is provided in Table 4.16.

First, the company has assumed revision surgery occurs more frequently in patients treated with FESS than with XprESS MSDS. Expert advice has indicated that there is no evidence to support any difference in revision surgery between treatment options over a 5 year period and the evidence from the REMODEL trial up to 18 months following surgery showed no significant difference between FESS and XprESS MSDS [4]. As such, the EAC has judged that modelling a difference in revision surgery over a 5 year period is not supported by the current evidence base.

Second, within its analysis the company assumed that the clinical data derived from the REMODEL study generalise to the decision problem outlined by NICE. As described in Section 3, patients within REMODEL had uncomplicated CRS maxillary sinus disease with or without anterior ethmoid disease [4], whilst the company has assumed that data generalise to all patients with CRS or RARS (i.e. the population defined in the scope). There are further weaknesses of the REMODEL study including the mix of devices used within the study and the high dropout rate creating attrition bias as described in Section 3. These weaknesses also apply when using evidence from REMODEL to populate the economic model.

Third, the cost of surgery under local anaesthetic for both FESS and XprESS MSDS was derived by applying a multiplier for hernia surgery to the cost under general anaesthetic. The company carried out bottom-up costing to determine the cost under general anaesthetic and deriving the cost under local anaesthetic in the same way would have been welcome. However, the EAC notes that the costs derived from the bottom-up costing approach for surgery under general anaesthetic could not be fully verified by the NICE ratified clinical experts. In particular, the surgery duration varied. This input is the key driver of the analysis and therefore has a material implication on the model's results. The EAC acknowledges that differences often arise from different expert advice and the associated underlying uncertainty surrounding these inputs cannot be resolved. Furthermore, the duration of hospital stay

taken from HES was not transparent and subject to the limitations described in Section 4.2.6.

In addition to the weaknesses regarding the input parameters used within the model, a number of weaknesses associated with the analysis itself were identified. First, an inconsistent cost year has been used throughout the model, in that all costs have not been inflated to the current cost year. For example, the cost of readmission to hospital is taken from at 2011/12 cost source and the cost of theatre time from a 2006 cost source. Inflating these costs to 2014/15 prices had a limited impact on the results of the model.

Second, no PSA has been carried out and no rationale for this provided. It is plausible that the company judged the value of this analysis to be limited given that the confidence level around many of the model's inputs is unknown. However, reasoning for the exclusion of PSA from the submission would have been welcome given that there is a section in the submission document on this type of analysis.

Finally, the company did not attempt to make any judgement regarding the comparative cost-effectiveness of XprESS MSDS compared to other balloon systems that are currently available within the NHS (e.g. Ventera sinus dilation system; LENIOflex; NuVent EM balloon sinus dilation system or Vent-Os sinus dilation system). Rather, an analysis was performed against a system no longer available within the NHS, albeit withdrawn very recently. The EAC recognises that there is very limited information (either clinical or price data) on alternative balloon systems. However, a narrative acknowledgement of the other systems available within the UK would have been welcome.

4.5 *Additional work undertaken by the External Assessment Centre in relation to economic evidence*

The EAC conducted a cost-consequence analysis comparing XprESS MSDS with FESS using the company's model with updated input parameters. The analysis was carried out by 1 health economist adapting the company's model and a second checking the adaptation. The full EAC analyses are described in the subsequent sections.

4.5.1 EAC's base-case inputs

As described in Section 4.2 the EAC disagreed with some of the input parameters and assumptions used by the company within its *de novo* cost analysis. The EAC revised the company's *de novo* model by updating a number of the input parameters to those specified in Table 4.16. The specific inputs that were changed were compared with the company's submission are highlighted within Table 4.16.

Table 4.16: EAC's input parameters

Variable	Company input	EAC input	Agrees with company's base case	Source and rationale
Cost of procedure: FESS (general anaesthetic)	£2,594	£657	✖	The procedure cost was derived through bottom-up costing detailed in Table 4.6.
Cost of procedure: XprESS MSDS (general anaesthetic)	£984	£428	✖	The procedure cost was derived through bottom-up costing detailed in Table 4.7.
Cost of procedure: FESS (local anaesthetic)	£1,636	£456	✖	The procedure cost was derived through bottom-up costing detailed in Table 4.9.
Cost of procedure: XprESS MSDS (local anaesthetic)	£620	£466	✖	The procedure cost was derived through bottom-up costing detailed in Table 4.10.
Cost of XprESS	£900	£900	✓	Derived from company's submission.
Cost of training on XprESS MSDS	£0	£5.50	✖	The cost was derived through bottom-up costing explained in Section 4.2.7.
Cost of FESS	£300	£300	✓	Derived from company's submission.
Proportion under local anaesthetic: FESS	0%	2%	✖	The proportion of surgery under local anaesthetic was derived from expert advice and in line with the company's scenario analysis.
Proportion under local anaesthetic: XprESS MSDS	0%	10%	✖	The proportion of surgery under local anaesthetic was assumed based on expert advice.
Pain medication: FESS	2.8 days	2.8 days	✓	The duration of pain medication was taken from REMODEL [4].
Pain medication: XprESS MSDS	1.0 day	1.0 day	✓	The duration of pain medication was taken from REMODEL [4].
Cost of pain medication	£0.13	£0.13	✓	The cost of pain medication was taken and verified from the company's model.
Requiring GP visits within 3 months of surgery: FESS	42%	42%	✓	National audit data were used to derive the proportion of patients requiring GP visits within 90 days of surgery in the absence of more recent data or

Variable	Company input	EAC input	Agrees with company's base case	Source and rationale
				data more specific to patients eligible for balloon therapy [4].
Requiring GP visits within 3 months of surgery: XprESS MSDS	24%	24%	✓	The relative risk of nasal bleeding at discharge from hospital from REMODEL (0.57) was applied to the FESS data from the national audit based on expert opinion [4, 15].
Number of GP visits in first 90 days for those visiting GP	1.861	1.861	✓	National audit data were used to derive the proportion of patients requiring GP visits within 90 days of surgery in the absence of more recent data or data more specific to patients eligible for balloon therapy [4].
GP visits in 5 years following surgery: FESS	0.12 per month	0.12 per month	✓	National audit data were used to derive the rate of GP visits in the 5 years post-surgery in the absence of more recent data or data more specific to patients eligible for balloon therapy [15].
GP visits in 5 years following surgery: XprESS MSDS	0.10 per month	0.10 per month	✓	The percentage difference in CRS events from REMODEL (-13.5%) was applied to the FESS data from the national audit [4, 15]. The experts indicated that this may be an appropriate indicator.
Cost of GP visit	£94.43	£46	✗	The mean of: blocked nose: £48.91; infection: £38.97 to £39.64; blocked nose and infection: £50 as reported in Table 4.8.
Readmission within 90 days of surgery: FESS	4.1%	4.1%	✓	National audit data were used to derive the risk of readmission with 90 days of surgery in the absence of more recent data or data more specific to patients eligible for balloon therapy [15].
Readmission within 90 days of surgery: XprESS MSDS	2.3%	2.3%	✓	The relative risk of nasal bleeding at discharge from hospital from REMODEL (0.57) was applied to the FESS data from the national audit based on expert opinion [4, 15].
Cost of readmission	£601	£902	✗	Weighted average of CA24A minor nose procedure as a day

Variable	Company input	EAC input	Agrees with company's base case	Source and rationale
				case or non-elective short stay [83].
Revision surgery up to 12 months: FESS	4.1%	1.7%	✗	The rate of revision surgery in the 12 months post-surgery was derived directly from REMODEL [4].
Revision surgery up to 12 months: XprESS MSDS	3.6%	1.4%	✗	The rate of revision surgery in the 12 months post-surgery was derived directly from REMODEL [4].
Revision surgery between 12 months and 5 years: FESS	2.9%	1%	✗	The annual rate of revision surgery beyond 12 months was crudely estimated at 1% per year from recent UK data [23]. The same rate is used for both arms based upon expert opinion.
Revision surgery between 12 months and 5 years: XprESS MSDS	2.5%	1%	✗	The annual rate of revision surgery beyond 12 months was crudely estimated at 1% per year from recent UK data [23]. The same rate is used for both arms based upon expert opinion.
Cost of revision surgery: FESS	£2,594	£998	✗	Assumed that the cost for revision surgery is equal to initial surgery weighted for local/general anaesthesia based on expert opinion. The cost of equipment of £300 is also added.
Cost of revision surgery: XprESS	£984	£432	✗	Assumed that the cost for revision surgery is equal to initial surgery weighted for local/general anaesthesia based on expert opinion. The cost of equipment of £900 is also added.

4.5.2 EAC's base case results

Using the EACs base case inputs, XprESS MSDS was found to incur costs of £330 per patient over a 5 year time frame compared with FESS. A full breakdown of the costs with both procedure types is provided in Tables 4.17 and 4.18.

Table 4.17: EAC's base case results by year

	XprESS MSDS	FESS	Cost saving per patient
Year 1	£1,440	£1,091	**-£349**
Year 2	£67	£72	**£5**
Year 3	£65	£69	**£5**
Year 4	£62	£67	**£5**
Year 5	£60	£65	**£4**
Total	**£1,694**	**£1,364**	**-£330**
* Note that the number in this table may not add/subtract exactly due to rounding.			

Table 4.18: EAC's base case results by component

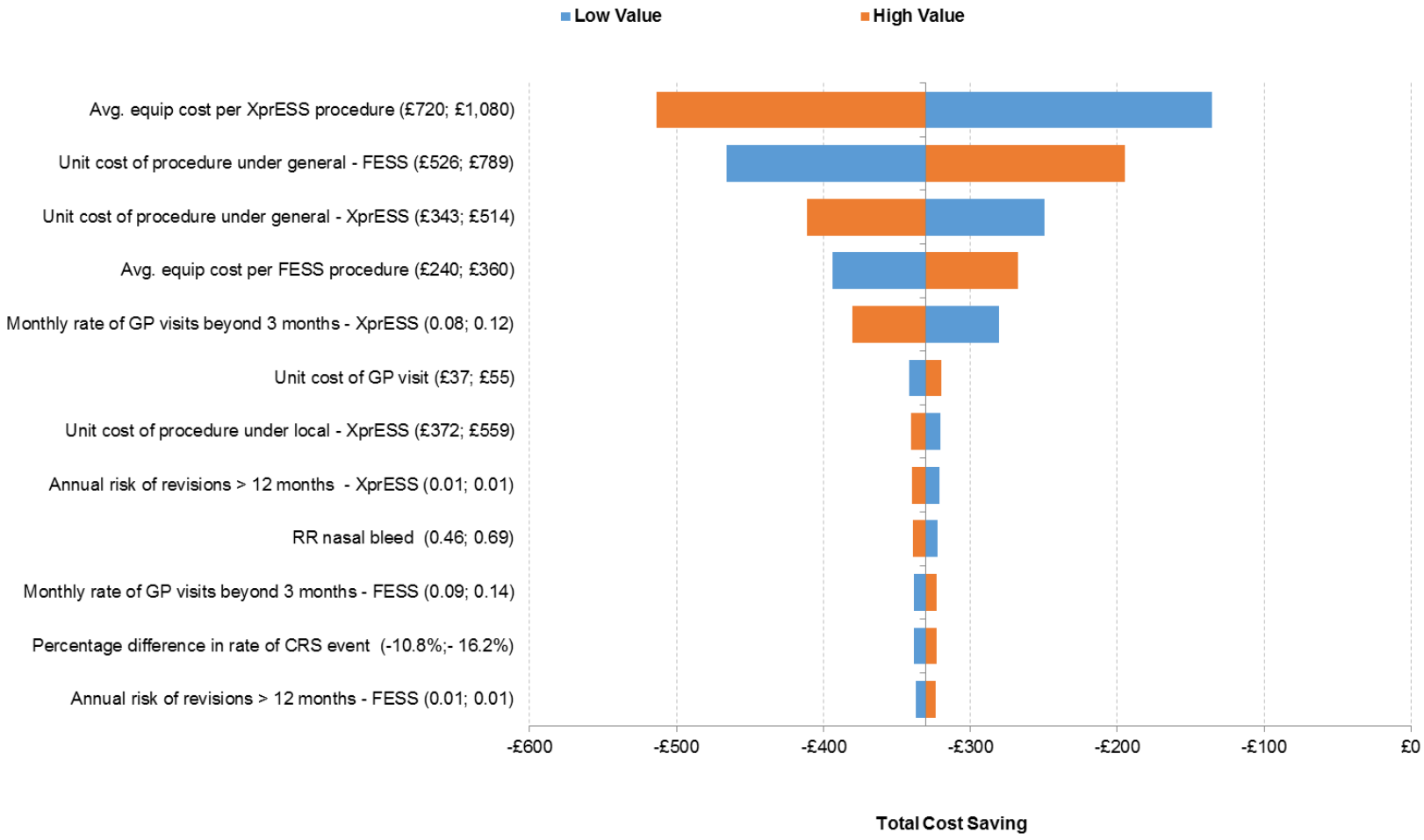
	XprESS MSDS	FESS	Cost saving per patient
Surgery excluding equipment	£432	£653	£221
Equipment (including training)	£905	£300	-£605
GP visits before 3 months	£21	£36	£15
Pain management	£0	£0	£0
Admissions before 3 months	£21	£37	£16
GP visits beyond 3 months	£249	£288	£39
Revisions	£66	£50	-£16
Total	**£1,694**	**£1,364**	**-£330**
* Note that the number in this table may not add/subtract exactly due to rounding.			

The EAC conducted sensitivity and scenario analyses as detailed in Sections 4.5.3 and 4.5.4. These included univariate DSA and multivariate DSA. PSA was not carried out given that the confidence around the majority of the included parameters was unknown, meaning the analysis would need to be based upon a substantial number of assumptions.

4.5.3 EAC's univariate DSA

The EAC conducted univariate sensitivity analysis around all model input parameters to determine the key drivers of the analyses. In line with the company, the EAC varied each input by ±20%. The results of this analysis were presented in a tornado diagram (Figure 4.6). Within this diagram, the results are presented such that the variation from the total incremental cost (between XprESS MSDS and FESS) is displayed. Only the 12 inputs with the greatest impact on the results are displayed to improve readability.

Figure 4.6: Tornado diagram based on EAC sensitivity analysis



The tornado diagram shows that in no instance does varying any input by ±20% change the direction of the results (i.e. FESS is always cost saving compared to XprESS). The key driver of the analysis is the equipment cost of XprESS MSDS. This input is set by Entellus Medical. It is not known if discounts are offered at a lower price. Other key drivers include the cost of each procedure under general anaesthetic. The key drivers in the EAC's analysis are consistent with those in the company's analysis.

To note, changing the cost of readmission has a very limited impact on the results of the model and is not in the 12 largest drivers of the analysis. Hence even if this cost is too high, it does not impact upon the results of the model. Threshold analyses were conducted around the key drivers of the analysis to determine how much variation would be required in order for XprESS MSDS to become cost saving versus FESS. Those costs of the XprESS device and FESS consumables per procedure were judged to be reasonably certain and hence were excluded from the threshold analysis. The key drivers considered within the threshold analysis are shown below. These include the components of surgery cost for FESS and XprESS MSDS procedures.

Duration of FESS procedure under general anaesthetic

Where the duration of FESS procedure is longer than 66 minutes (compared with 42.5 minutes in the base case) the direction of the results change, meaning XprESS MSDS becomes cost saving (Figure 4.7). Within the company's submission the duration of FESS was judged to be 90 minutes, although the definition of the time period was not stated. This value was informed by expert advice who considered the time taken to treat multiple sinuses in one episode of care. The EAC's estimation of surgery duration was based upon expert advice who quoted the duration for treating multiple sinuses. The EAC's experts provided the time for FESS for patients with equivalent severity of CRS to those eligible for FESS. Where experts provided FESS durations that were longer than 66 minutes these were based upon patients with more severe CRS who would not be eligible for balloon therapy.

The experts utilised by both the company and the EAC are have published widely within the area of CRS and have contributed to relevant clinical guidelines [21, 22].

Alternate sources suggest that the duration of FESS is similar to that specified by the EAC's experts. The national audit specified 39.6 minutes per procedure ('knife to skin' to descrubbing) based upon all patients undergoing surgery within the UK, or 41.5 minutes for patients without polyps. Therefore this duration should reflect both those patients undergoing unilateral procedures and those undergoing procedures in multiple sinuses [15]. A HTA report

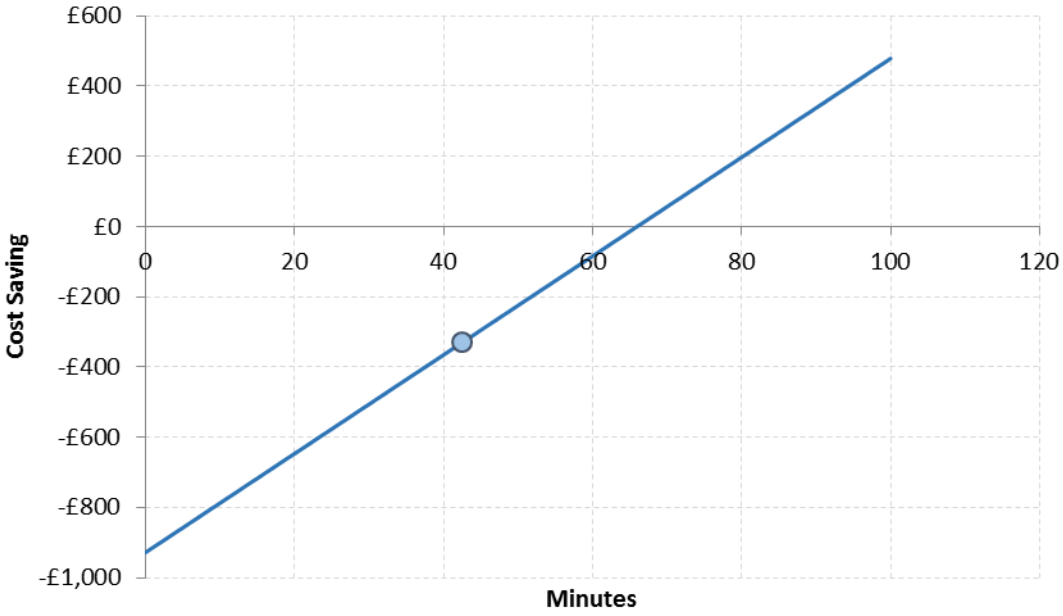
specified that based on 1 surgeon, surgery takes 46 minutes [16] (definition unknown). Within this study it is reported that the procedure time varies by patients' characteristics, extent of disease, experience of the surgeon and how meticulous surgeons are in polyp removal. The number of sinuses treated within this estimate is not reported, hence it is assumed to be an average.

The company reported within Section 9.4.3 of their submission that Hopkins *et al.* (2006) reported FESS duration for unilateral procedures of 42 minutes. Within this paper by Hopkins *et al.* (2006) the mean surgical time is reported to be 40 minutes [17]. This time is not specified to be for unilateral procedures only. The EAC asked the company to substantiate this claim. The company reported that this claim was an error within the submission and an alternative reference should have been provided (correspondence log, page 24). Within the alternative source, a Dutch study, FESS with traditional methods is compared with FESS with a microdebrider and all operating times quoted are for unilateral procedures [87]. Operating time is reported to be a median of 30 minutes (inter-quartile range (IQR): 22-39 minutes) with a microdebrider and 41 minutes (IQR: 28 – 49 minutes) [87]. The company reported within its submission that operating on 2 sinuses was assumed to double the procedure time; however, no source was provided for this.

The company conducted a scenario analysis using data from an Italian RCT, which compared an alternative balloon dilation system to FESS in patients undergoing frontal sinus surgery. The company reported within its submission that procedures of the frontal sinuses take longer than other sinuses. Within this study, FESS took a mean of 65 minutes (±15 minutes) and balloon dilation 32 minutes (±7 minutes) [88]. Whilst the FESS procedure time reported within this study is longer than that utilised by the EAC, it is not long enough to change the direction of the results and is based on a subset of patients undergoing sinus surgery.

The EAC judged that the UK sources, namely the national audit data reported in 2 publications [15, 17], the estimate provided within the HTA [16] and the information provided to the EAC by experts, were the most representative data of patients undergoing FESS within the NHS. These sources consistently reported procedure times for FESS of between 40 and 46 minutes. None of the sources identified by the EAC or cited by the company reported a FESS duration long enough to change the direction of the results.

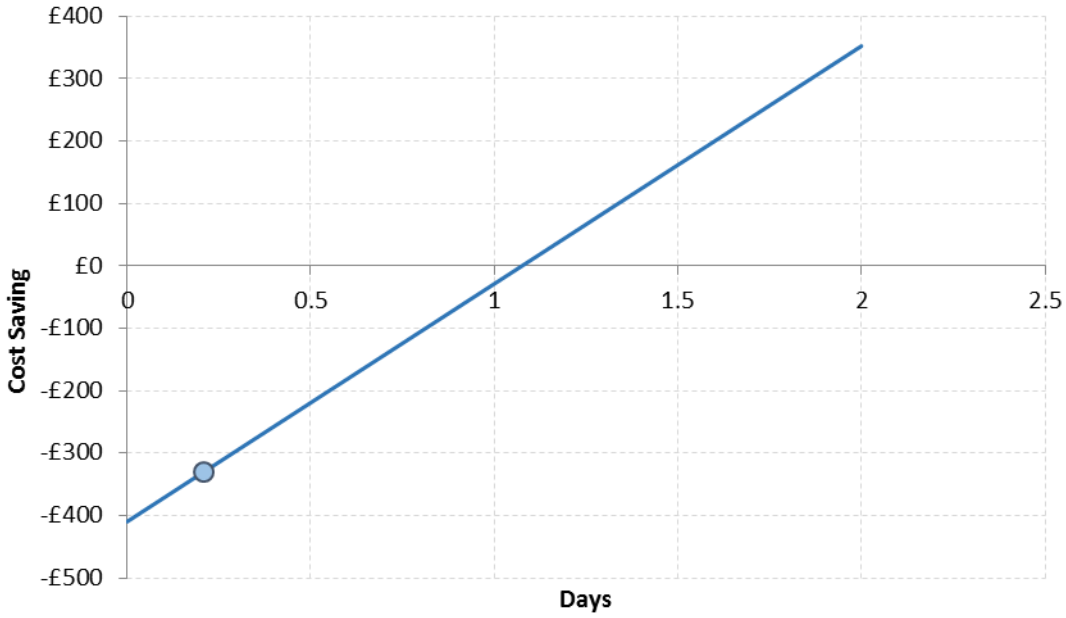
Figure 4.7: Univariate sensitivity analysis around duration of FESS



Duration of hospital stay after FESS under general anaesthetic

Where the duration of the hospital stay following FESS is longer than 1 day (compared with 5 hours in the base case) the direction of the results change, meaning XprESS MSDS becomes cost saving (Figure 4.8). Should a substantial proportion of FESS patients require an overnight stay, XprESS MSDS has the potential to be cost saving. All experts advised FESS is carried out as a day case in most instances. Therefore, it is unlikely that the average duration of hospital stay for those patients also eligible for treatment with XprESS MSDS would be longer than 1 day.

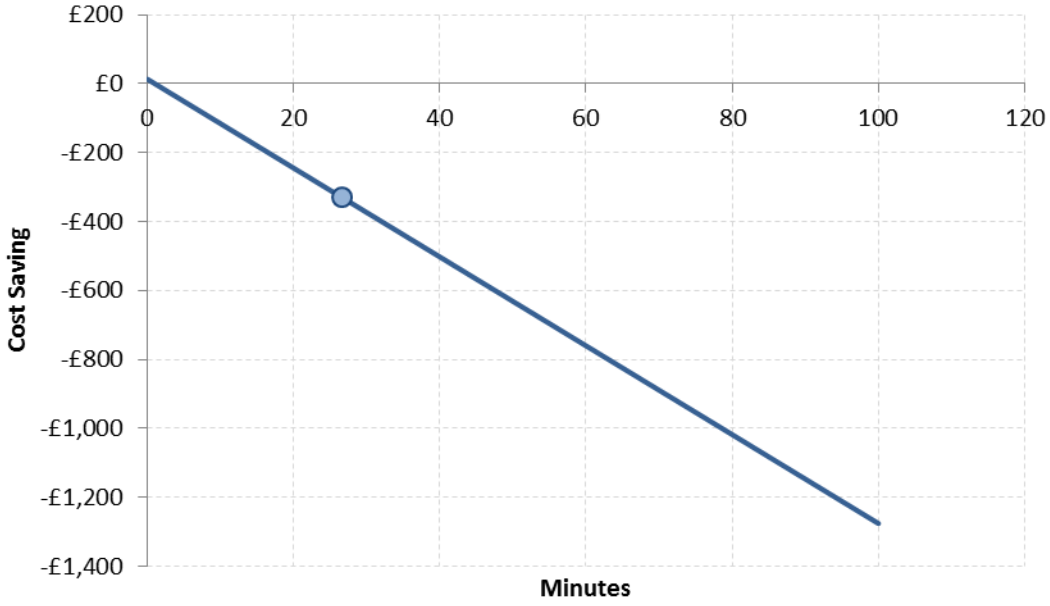
Figure 4.8: Univariate sensitivity analysis around hospital stay following FESS



Duration of XprESS MSDS procedure under general anaesthetic

The model's results are not sensitive to the duration of surgery with XprESS MSDS. This needs to be as low as 0 minutes for the direction of the results to change, as shown in Figure 4.9.

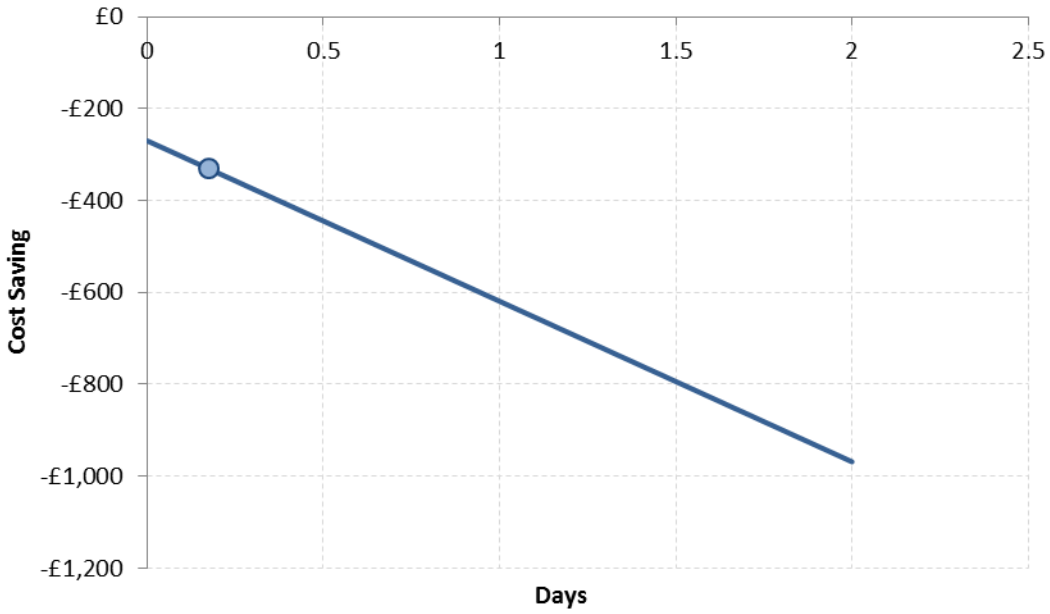
Figure 4.9: Univariate sensitivity analysis around duration of XprESS MSDS procedure



Duration of hospital stay after XprESS MSDS procedure under general anaesthetic

The model's results are also not sensitive to the duration of the hospital stay after surgery with XprESS MSDS. Even at a duration of 0 days the direction of the results of the model do not change, as shown in Figure 4.10.

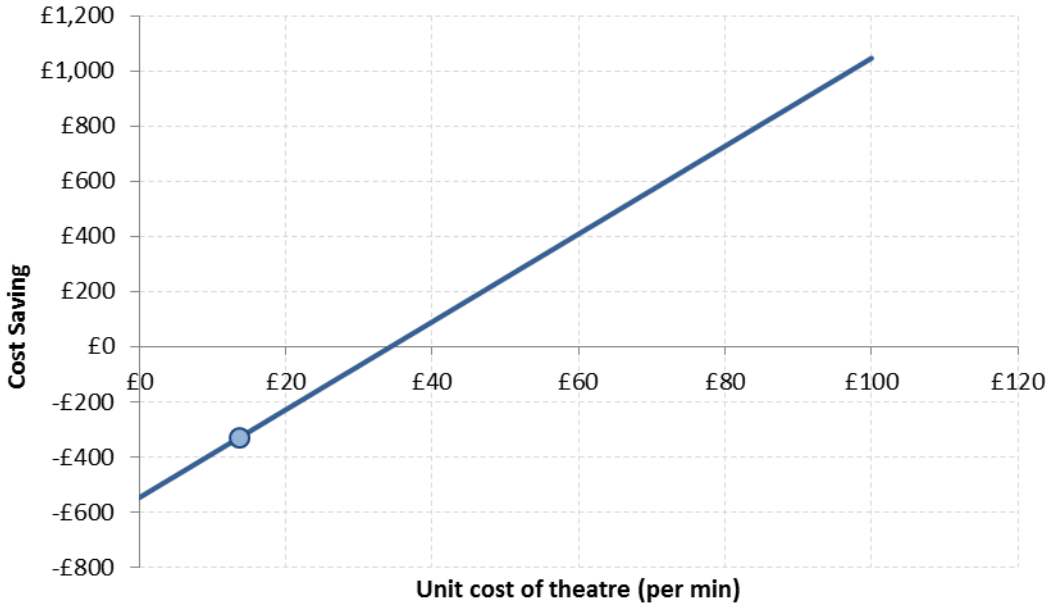
Figure 4.10: Univariate sensitivity analysis around hospital stay following XprESS MSDS procedure



Unit cost of theatre time

Where the unit cost per minute of a theatre is above £34 (£2,040 per hour), the direction of the results of the model change such that XprESS MSDS becomes cost saving (Figure 4.11). This change occurs because patients undergoing FESS have a longer procedure time than those having surgery with XprESS MSDS, meaning that an increase in the cost of the theatre time will have a larger impact on the FESS arm of the model. The company used a theatre cost of £20 per minute (£1,200 per hour), exclusive of surgeon (£1.77 per minute) and nurse (£1.47 per minute) totalling £23.24 per minute (£1,394 per hour). This is well below the threshold value of £34 (£2,040 per hour). In addition, in the breakdown of ENT costs provided by ISD Scotland, no Scottish Board has a cost per minute as high as £34 [81]. A further theatre cost identified by the EAC through targeted searching reported a cost of £1,176 per hour, or £19.60 per minute [89]. However, this cost is not specific to ENT surgery and is therefore likely to be less specific than the ISD Scotland cost.

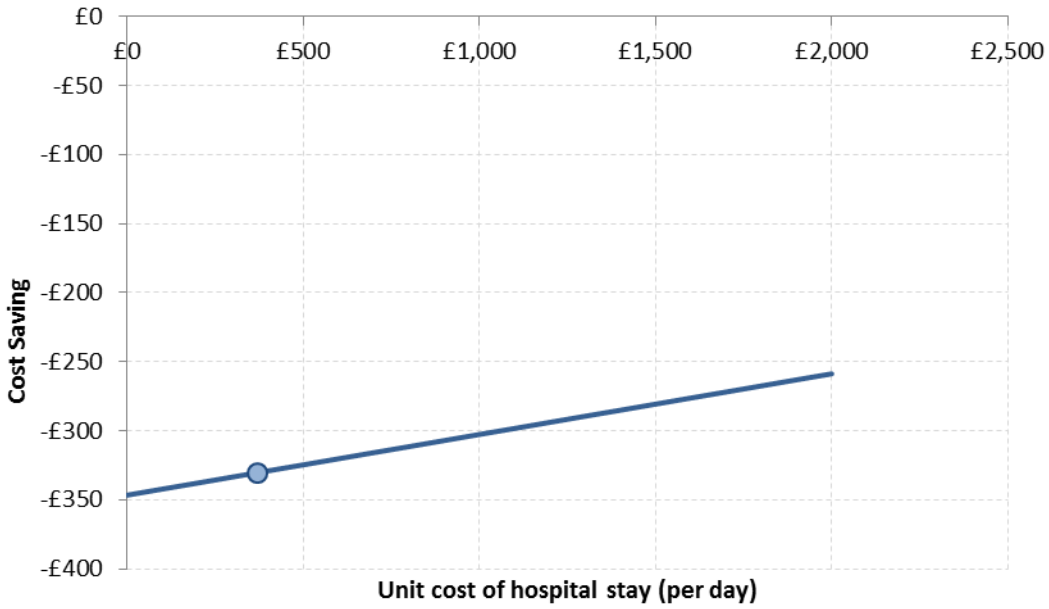
Figure 4.11: Univariate sensitivity analysis around theatre cost per minute



Unit cost of hospital stay

The model's results are not sensitive to the unit cost per day of hospital stay (Figure 4.12). Varying this input parameter makes very little difference to the results of the model. A higher unit cost per day in hospital does reduce the cost incurrence of XprESS MSDS somewhat due to the longer hospital stay following FESS. However, this cost would need to be unreasonably high to change the direction of the results.

Figure 4.12: Univariate sensitivity analysis around cost per hospital stay



4.5.4 EAC's scenario analyses

EAC analysis using length of stay data from HES

A scenario analysis was conducted using the length of stay data taken from HES as reported in the company's submission. Within this scenario patients remained in hospital for 0.97 days after FESS and 0.43 days after the procedure with XprESS MSDS. Whilst the data from HES are subject to the limitations specified in Section 4.2.6, this uncertainty around the expert's responses was explored through this scenario.

The results generated in this scenario are displayed in Table 4.19. These show that the difference in costs between FESS and XprESS MSDS is lower than in the base case. However, XprESS MSDS remains cost incurring.

Table 4.19: Scenario using length of stay data from HES

	XprESS MSDS	FESS	Cost saving per patient
Total	£1,797	£1,661	**-£136**

EAC analysis using office cost of procedure under local anaesthetic

A scenario analysis was conducted whereby the cost of using XprESS MSDS under local anaesthetic was incurred based upon the procedure being carried out in an office setting. Therefore, no theatre costs were included. The bottom-up costing approach is shown in Table 4.20.

Table 4.20: Bottom-up costing for XprESS in an office setting

Component	Value	Source and explanation
Length of procedure	31.7 minutes	Clinical experts. Average of 3 experts providing advice on both FESS and XprESS MSDS (20, 30 and 45 mins).
Cost per minute of surgeon	£1.77	PSSRU [77].
Cost per minute of nurse	£1.47	PSSRU [77].
Gowns and tray	£115	Company's submission comprising gowns for 2 people and 1 tray.
Length of stay in hospital	2.17 hours (0.09 days).	Clinical experts. Average of 3 experts providing advice on both FESS and XprESS MSDS (3, 2 and 1-2 hours).
Cost per day in hospital	£369.64	NHS reference costs 2014-15: elective inpatient excess bed day[83].
Total cost	**£251**	

Under this scenario, the proportion of patients having the procedure under local anaesthetic was varied. All other input parameters remained as in the base case.

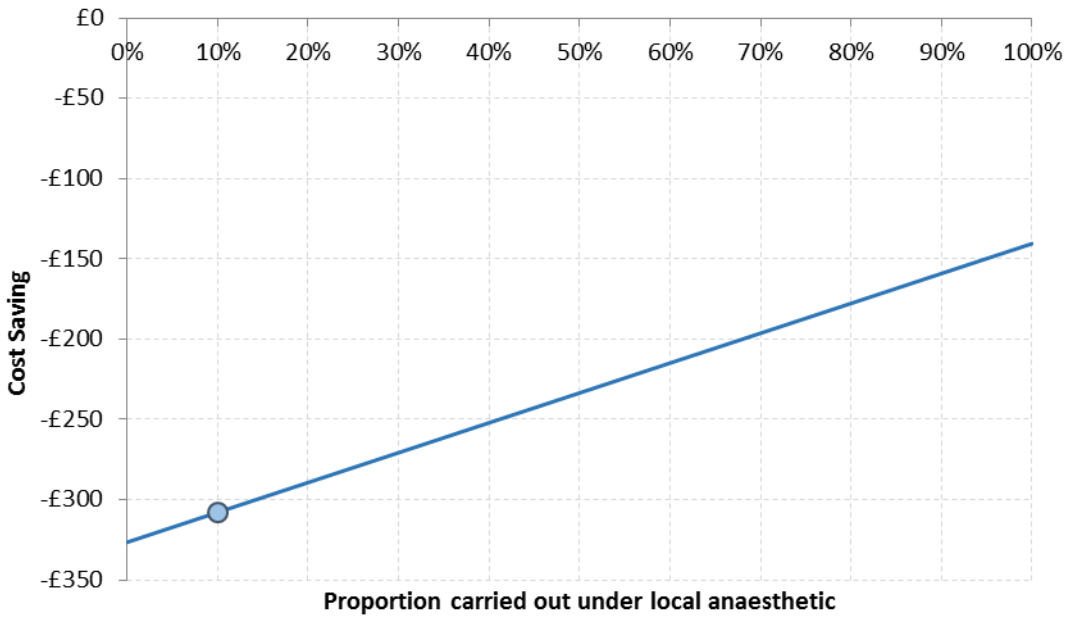
The results of this scenario whereby 10% of patients underwent surgery under local anaesthetic are shown in Table 4.21.

Table 4.21: Scenario whereby XprESS MSDS is used in an office setting

	XprESS MSDS	FESS	Cost saving per patient
Total	£1,672	£1,364	**-£308**

Further analyses were carried out whereby the proportion of patients having the procedure under local anaesthetic was varied also. The results of this analysis are shown in Figure 4.13. This shows that even where all patients undergo the procedure with XprESS MSDS in an office setting under local anaesthetic, cost savings are not generated.

Figure 4.13: Proportion of procedures carried out in office under local anaesthetic



EAC analysis using company's general/local anaesthetic cost ratio

A scenario was considered whereby the cost of each of the procedures under local anaesthetic was determined using the ratio of 0.631 derived by the company within their submission based upon hernia procedures. Using this ratio with the EAC's cost under general anaesthesia mean that the following costs can be estimated:

- XprESS MSDS under local anaesthetic = £270
- FESS under local anaesthetic = £415

The results generated in this scenario are displayed in Table 4.22. These show that the difference in costs between FESS and XprESS MSDS is lower than in the base case. However, XprESS MSDS remains cost incurring.

Table 4.22: Scenario using company's general/local anaesthetic cost ratio

	XprESS MSDS	FESS	Cost saving per patient
Total	£1,674	£1,363	**-£311**

EAC analysis using alternative rate of revision

Within the EAC's base case analysis, the rate of revision surgery in years 2-5 was estimated to be 1% for all patients. This rate is lower than that used by the company and also than that reported by Hopkins and colleagues in paper describing long term outcomes from the national audit [72]. Therefore, the EAC has conducted a scenario analysis using the rate reported by Hopkins *et al.* (2009): 15.5% at 5 years. Within this scenario the rate of revision surgery for both FESS and XprESS remained constant (based on EAC expert advice). The annual rate of revision surgery in years 2-5 is estimated to be 3.5%. This was generated by taking the rate of revision in year 1 (average of around 1.5%) from the 15.5% and dividing the remainder by 4.

The results generated in this scenario are displayed in Table 4.23 showing that varying the rate of revision surgery in years 2 to 5 has a limited impact upon the results of the model. The savings with FESS increase because revision surgery is more expensive with XprESS MSDS than FESS due to the higher equipment cost.

Table 4.23: Scenario using alternative rate of revision

	XprESS MSDS	FESS	Cost saving per patient
Total	£1,808	£1,445	**-£363**

EAC analysis inclusive of hospital appointment for debridement

One expert advised that in his practice post-surgery debridement for patients undergoing FESS is standard practice at 1 week after surgery. Debridement is not carried out for patients undergoing the procedures with XprESS MSDS. All other experts advised that debridement is not routinely conducted in any patients. Published evidence suggests practice in surgical debridement is varied post FESS [90]. Given that 1 expert reported that a follow-up appointment for debridement is standard, a scenario analysis has been conducted to include the cost of this appointment in the FESS arm of the model.

The cost of an appointment for debridement was taken from NHS reference costs (2014/15) and the following code used: CA29Z (ENT) minor sinus procedure as an outpatient procedure = £162. This cost was applied to all patients undergoing surgery with FESS within this scenario.

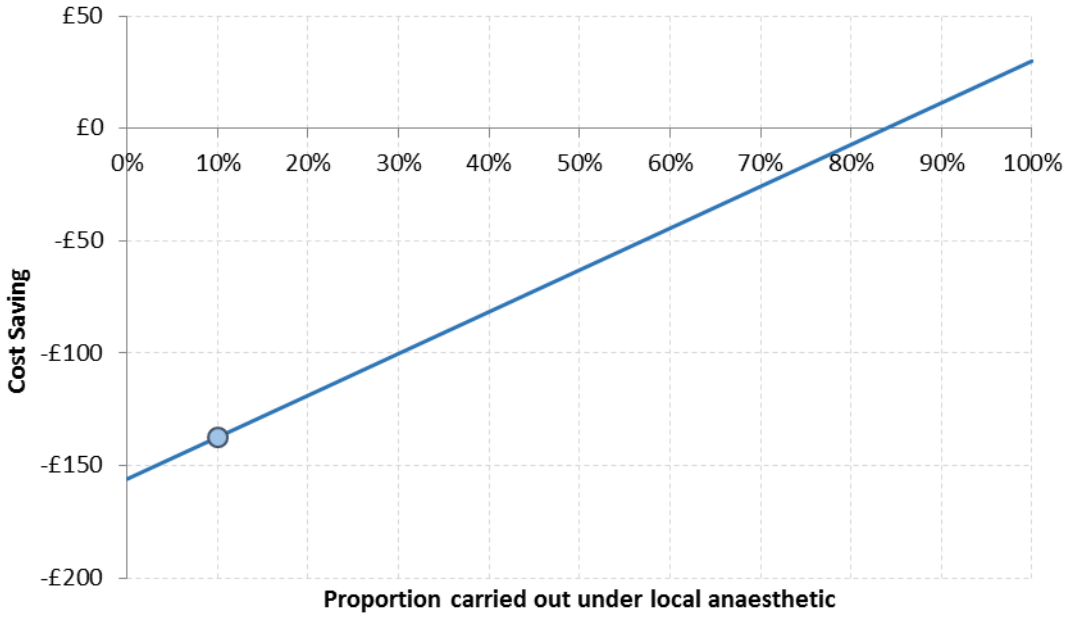
The results generated in this scenario are displayed in Table 4.24. These show that the difference in costs between FESS and XprESS MSDS is lower than in the base case due to the additional cost of the debridement appointment. However, XprESS MSDS remains cost incurring.

Table 4.24: Scenario with appointment for debridement

	XprESS MSDS	FESS	Cost saving per patient
Total	£1,672	£1,535	**-£137**

This scenario was explored further to estimate the cost implications of comparing XprESS MSDS procedures in an office setting under local anaesthetic to FESS, whereby FESS patients have a second hospital visit for debridement. This scenario was considered as it met the situation in the Trust of 1 of the experts. The results are presented in Figure 4.14. Under this scenario, XprESS MSDS has the potential to generate cost savings where over 80% of procedures can be conducted in an office setting under local anaesthetic.

Figure 4.14: Proportion of procedures carried out in office under local anaesthetic where FESS patients have debridement appointment



EAC analysis using consistent proportion of patients visiting the GP (first 90 days post-surgery)

Two experts advised that post-surgery nasal bleeding was not a good predictor of GP visits up to 90 days following surgery. All other experts advised that post-surgery nasal bleeding was a good predictor. Given the divided opinion, a scenario analysis has been conducted by the EAC that uses the same number of patients having GP visits in the first 90 days post-surgery for XprESS MSDS and FESS. The FESS rate of 42% (taken from the national audit [15]) was used in both arms of the model.

The results generated in this scenario are displayed in Table 4.25. These show that having an equal number of GP visits in the first 3 months does not change the direction of the result, rather the XprESS MSDS becomes increasingly cost incurring.

Table 4.25: Scenario using equal number of GP visits in first 3 months post-surgery

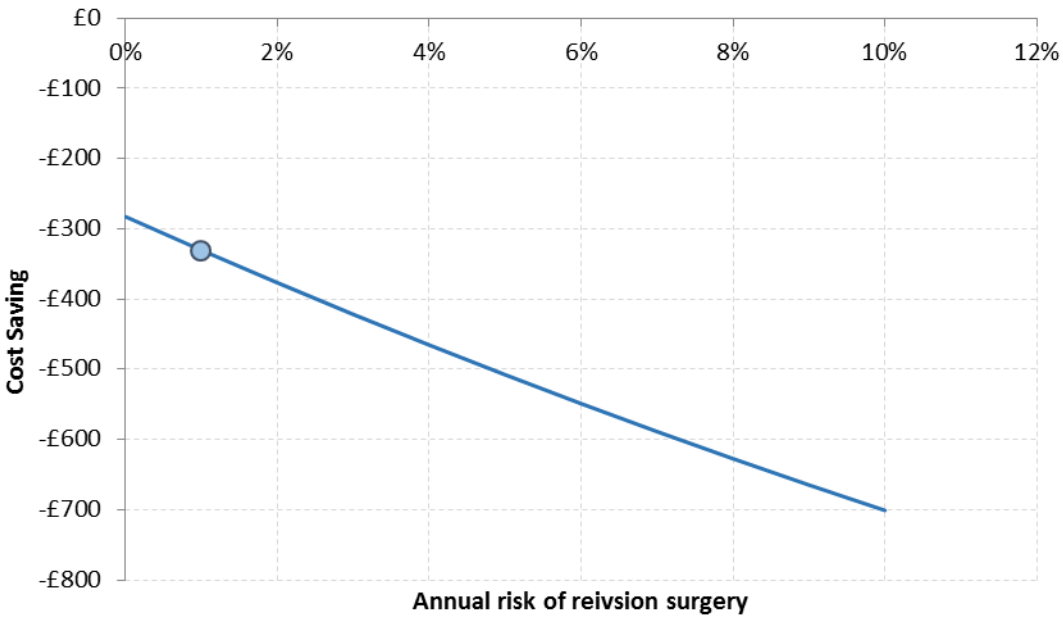
	XprESS MSDS	FESS	Cost saving per patient
Total	£1,710	£1,364	**-£346**

EAC sensitivity analysis on rate of revision surgery for XprESS MSDS (2-5 years post-surgery)

Experts were divided as to whether an increase in revision rate at 12 months would be a good indicator of revision rates up to 5 years. Two experts specified that they expected revision rates to be higher with XprESS MSDS with1 expert providing data demonstrating this. The EAC conducted threshold analysis to determine the rate of revision surgery for XprESS 2-5 years post-surgery at which the direction of the results would change.

The results are presented in Figure 4.15. This shows that where the annual rate of revision surgery for XprESS MSDS increases (compared with 1% for FESS), XprESS MSDS becomes increasingly cost incurring. Data from 1 expert shows that in his Trust revision rates are 20% for XprESS MSDS and 3% for FESS. However, the sample of patients undergoing surgery with XprESS MSDS is low (around 6 patients per year).

Figure 4.15: Variation of revision rate 2-5 years after surgery with XprESS MSDS



4.6 *Conclusions on the economic evidence*

The company included 6 economic evaluations within its cost-effectiveness review. The EAC deemed all 6 to be outside the scope of the decision problem because XprESS MSDS, or indeed any balloon dilation system currently available within the UK NHS, was not an intervention considered within any of the evaluations [28, 65-68, 70]. The EAC did not identify any economic evaluations reporting on XprESS MSDS or other balloons systems available within the NHS. Therefore, no conclusion can be drawn regarding any published evidence reporting on the cost-effectiveness of XprESS MSDS.

The *de novo* model submitted by the company was fully executable and captured the differences in treatment with XprESS MSDS and treatment with FESS, thus providing an answer to the decision problem set out in the scope. A comparison was also provided against the Acclarent device – a balloon dilation system used previously within the NHS, but no longer available (see correspondence log, appendix 3). The model took a 5 year time horizon and comprised a decision tree and Markov model element. The first year post surgery was modelled using the decision tree whereby patients were at risk of a GP visit, a readmission to hospital or revision surgery. The subsequent years were modelled through the Markov model using annual cycles and 2 health states: revision surgery and successful surgery. Patients were only able to have revision surgery once during the time span of the model; hence revision surgery was an absorbing health state. Patients incurred costs in the model through the following: initial surgery resource use and equipment, post-surgery pain medication, GP visits, readmission to hospital and revision surgery. In the base case all patients were assumed to undergo surgery with general anaesthesia.

In the company's base case, XprESS MSDS was estimated to generate cost savings of £1,302 per person compared with FESS. These cost savings were largely generated through a reduction in procedure cost with XprESS MSDS due to shorter surgery duration (30 minutes versus 90 minutes). Univariate DSA was carried out around all model input parameters. XprESS MSDS was found to become cost incurring where the duration of surgery with the balloon dilation systems was greater than 80 minutes or where the duration of FESS was shorter than 41 minutes.

The EAC critically appraised the model and the accompanying narrative in the company's economic submission. We accept the company could not conduct a comparison of XprESS MSDS to any balloon systems *currently* available within the NHS because there are very limited data available for such systems.

We also agree it was not possible to independently model the subgroups listed within the scope issued by NICE because of paucity of data.

Regarding the *de novo* model submitted by the company, the EAC judged that the structure was largely accurate and captured the key aspects of the disease area. However, the EAC noted that there were a couple of minor inappropriate structural issues (namely the use of an inconsistent cost year and the lack of justification for omitting PSA), which were each deemed to have a limited impact on the model's results. Of greater importance were the assumptions made around the data used to populate the model. Each input used by the company was considered and validated by the EAC where possible using expert advice and pragmatic literature searching. The EAC highlighted the following issues:

- Relative risks derived from the REMODEL trial were applied to FESS data from a national audit conducted in 2003 in order to determine the risk of revision surgery (up to 12 months and 2-5 years); risk of GP visit (up to 3 months and 3 months-5 years) and risk of readmission [4, 15]. The EAC judged that the population included within the national audit was broader than the population suitable for treatment with XprESS MSDS. Therefore, increasing the risk of each of the events above based on the baseline national data is not an accurate reflection of the patients within the scope. Hence, the EAC recommended using data from REMODEL directly as far as possible [4].

- The cost of surgery with either procedure under general anaesthetic was derived by the company through bottom-up costing. Whilst generally accurate, not all components could be validated by the EAC. The EAC therefore conducted their own bottom-up costing based upon targeted searching of the literature, national datasets and expert advice.

- Within the company's base case, all patients underwent surgery under general anaesthetic. This conservative assumption made by the company may underestimate the potential cost savings with XprESS MSDS. Based on expert advice the EAC deemed that a greater proportion of XprESS MSDS patients undergo surgery under local anaesthetic compared with FESS patients (10% versus 2%). Within the company's scenario analysis a proportion of patients underwent surgery under local anaesthetic. The cost of this procedure was determined by applying a ratio for hernia surgery costs under local versus general to the company's cost under general anaesthesia. The EAC's preference is to adopt a bottom-up costing approach for surgery under local anaesthesia. Furthermore, the EAC judges that the small cost of training surgeons on the device should have been included.

The EAC updated a number of model inputs (detailed in Table 4.16) and re-ran the company's model. The EAC's base case result estimated that XprESS MSDS is cost incurring by £330 per patient compared with FESS. The impact of each change that was made by the EAC is shown in Table 4.27. The EAC conducted univariate sensitivity analysis which identified the cost of the devices are the key drivers of the analysis (see Figure 4.6). In addition the EAC conducted a number of threshold and scenario analyses which showed the model's result to be generally robust over the scenarios considered (see Sections 4.5.3 and 4.5.4).

The change in result between the EAC's model and company's model was largely driven by the following inputs, where further discussion is warranted:

- Duration of FESS: the model's results are highly sensitive to the duration of FESS under general anaesthetic. Where the duration of FESS is longer than 66 minutes (compared with 42.5 minutes in the EAC's base case) the direction of the results change, meaning XprESS MSDS becomes cost saving. There is variability in the reported duration of FESS with the clinical experts used by the company reporting 90 minutes and the clinical experts that the EAC contacted reporting a mean duration of 42.5 minutes. The national audit specified 39.6 minutes per procedure for all patients and 41.5 minutes for patients without polyps [15] and a HTA report specified that surgery takes 46 minutes [16]. Given that there is no RCT data available for this input in a group of patients matching those specified in the scope the value for this input parameter relies heavily on expert opinion. It is likely that there is variation within practice which contributes to the uncertainty around this input parameter. However, the EAC judges that based on the evidence available to it the plausibility of FESS taking longer than 66 minutes in patients eligible for balloon dilation therapy is low. Further research would be required to ascertain this input parameter with more certainty.

- Unit cost of operating theatre: the results of the model are sensitive to the unit cost of the operating theatre per minute. Where this cost, inclusive of staff and general consumables, is above £34 per minute XprESS MSDS is estimated to be cost saving. However, based on the sources identified by the EAC, which include data from ISD Scotland [81], data from1 Welsh Trust [89] and the value used within the company's submission from NHS Institute for Innovation and Improvement [80] the plausibility of the cost per minute being above £34 per minute is low.

Under 1 of the scenarios considered, XprESS MSDS is estimated to generate cost savings compared with FESS. Where XprESS MSDS is used under local anaesthetic in an office setting in over 80% of cases and where FESS

patients typically have an appointment for debridement which would no longer be required, there is a potential for cost savings. The plausibility of this scenario in practice will depend on whether logistics within a hospital facilitate the procedure being carried out in an outpatient setting. One expert advised the EAC that he typically carries out debridement in FESS patients 1 week after surgery, but that this is not required with balloon therapy. The same expert advised the EAC that he sees the benefit of XprESS MSDS to be for those patients who are able to have the procedure in an outpatient (or office) setting. In these situations the device has the potential to generate cost savings, specifically where the need for debridement is removed and the device is used within an outpatient setting under local anaesthetic.

The EAC considers that the company put forward a generally well-considered economic case for XprESS MSDS versus FESS, showing potential cost savings. However, the EAC were unable to validate the key driver of the company's analysis, the procedure time with FESS. Based upon the EAC's best estimate, the EAC considers that the device is likely to be cost incurring compared to FESS in most scenarios. The EAC's conclusions are driven by a reduction in FESS procedure time which was based upon expert advice and confirmed by audit data [15, 17] and a HTA report [16]. There does, however, remain a gap in the evidence base regarding procedure times for both FESS and XprESS MSDS in directly comparable patients and the length of stay in hospital for these patients. Further research addressing these gaps would reduce the uncertainty in both the EAC's and company's results.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The additional work undertaken by the EAC around the parameters within the model changed the results as shown in Table 4.26. The direction of the results changed between the company's and EAC's base case analyses.

Table 4.26: Base case results; Company and EAC

	Company's base case	EAC base case
Total cost per patient with XprESS	£2,679	£1,694
Total cost per patient with FESS	£3,981	£1,364
Cost saving per patient	£1,302	-£330

Table 4.27 shows the cost impact of each action the EAC undertook to change the company's *de novo* model. The effect of each change is compared against the company's base case saving of £1,302 per patient. Most of the changes made by the EAC had a limited impact upon the result of the model. The actions with the greatest impact were the change in the cost of initial surgery with either XprESS MSDS or FESS.

Table 4.27: Impact of key changes to the *de novo* model

Action	Cost saving per patient	Change from company's base case	Percentage of base case cost saving	Impact of action (compared with the company's base case cost saving of -£1,302 per patient)
Revision surgery up to 12 months taken from REMODEL directly for both FESS and XprESS MSDS	£1,301	-£1	99.9%	The cost saving reduced very slightly due to the lower proportion of revision surgery in both arms, hence a lower overall difference.
Revision surgery 1-5 years set to 1% for both FESS and XprESS MSDS	£1,218	-£84	93.5%	The cost saving reduced due to the revision rate being set equal for XprESS MSDS and FESS (previously more revisions occurred with FESS).
Proportion of XprESS MSDS procedures under local anaesthetic set to 10%	£1,338	£36	102.8%	The cost saving increased as a proportion of XprESS MSDS patients now undergo cheaper surgery under local anaesthesia.
Proportion of FESS procedures under local anaesthetic set to 2%	£1,276	-£26	98.0%	The cost saving reduced as a proportion of FESS patients now undergo cheaper surgery under local anaesthesia.
Procedure cost: XprESS MSDS updated including training cost (under general anaesthetic)	£1,914	£612	147.0%	The cost saving increased substantially as the cost of surgery with XprESS MSDS has been reduced to the lower EAC value.
Procedure cost: FESS updated (under general anaesthetic)	-£901	-£2,203	-69.2%	The cost saving reduced substantially and direction of results changed as the cost of FESS has been reduced to the lower EAC value.
Cost of GP visit updated	£1,244	-£58	95.5%	The cost saving reduced slightly as more FESS patients incur GP visits, hence reducing this cost has a greater impact on the FESS arm.
Cost of readmission updated	£1,307	£5	100.4%	The cost saving increased slightly as more

Action	Cost saving per patient	Change from company's base case	Percentage of base case cost saving	Impact of action (compared with the company's base case cost saving of -£1,302 per patient)
				FESS patients are readmitted, hence increasing this cost has a greater impact on the FESS arm.
Cost of revision surgery updated for FESS and XprESS	£1,102	-£200	84.6%	The cost saving reduced as more FESS patients have revision surgery, hence reducing this cost has a greater impact on the FESS arm.
All above changes made simultaneously (EAC base case)*	**-£330**	**-£1,634**	**-25.3%**	The change in reduction in cost savings is driven heavily by the reduction in the cost of FESS within the EAC's base case analysis.

5 Conclusions

The current evidence based clinical guideline (EPOS) utilised by ENT surgeons specify that there is an evidence base to show that FESS is effective and safe for the management of patients with CRS who have failed medical treatment [21]. Expert advice confirmed that FESS is the main surgical intervention in these patients within the NHS.

XprESS MSDS is a standalone single-use balloon dilation catheter system used to treat CRS. The device takes a trans-nasal approach, which is made possible through the use of endoscopy and by the fact that the distal end of the XprESS MSDS is re-shapeable. The EPOS guideline states that at the time of its publication (2012) there was not enough data to support the use of balloon catheters as an alternative to FESS [21]. A more recent, NICE accredited, commissioning guide, published 2013, on rhinosinusitis, did not address the use of balloon dilation therapy [22]. This guide is due for update in September 2016.

The company, Entellus Medical, has presented its clinical evidence and economic case to support the adoption of the use of XprESS MSDS in people with CRS, including RARS, in whom maximal recommended medical therapy has failed.

The clinical evidence for XprESS MSDS comprises 1 RCT (REMODEL) that compared XprESS MSDS or its predecessor FinESS system with FESS. This study was published in 3 peer-reviewed papers at follow-up times of 6 months [2], 12 months [3], and up to 24 months [4]. Additionally, a series of single-arm observational studies reported on XprESS MSDS or the FinESS system [6-10, 12]. Evidence on both systems from the RCT and observational studies were synthesised in a published meta-analysis [4].No evidence was identified by the company comparing XprESS MSDS to other balloon systems. No additional studies suitable for inclusion were identified by the EAC.

The EAC judged that the most robust evidence relating to the outcomes specified in the scope was derived from the REMODEL trial [4]. The internal validity of the study was generally acceptable, but was compromised by the high initial attrition rates in the FESS arm immediately following randomisation, and the subsequent requirement for modified ITT analysis. The study was conducted in the US and included adult patients with uncomplicated CRS or RARS caused by maxillary sinus disease with or without anterior ethmoid disease. This gives rise to potential differences between the US and English settings, for example in:

- Clinical care pathways and delivery settings.

- Definition of maximal medical treatment.
- Baseline risks for the treated population.
- Specific indications for FESS and balloon dilation.

These issues also apply to the observational studies reported, with some studies (including the REMODEL trial) including results from the FinESS system. Hence the EAC has concerns about the generalisability of the results from the included studies to the populations managed in the NHS.

Evidence on change in rhinosinusitis symptoms and their impact was available from 6 studies reported on in 9 publications [2-4, 6-8, 10, 12]. These studies all used the SNOT-20 score, a disease specific QoL measure, as their primary outcome. The REMODEL trial reported a statistically significant and clinically important reduction in SNOT-20 compared with baseline of −1.67±1.10 (SD) for balloon dilation and −1.60±0.96 for FESS after 6 months (primary outcome) [2]. These improvements were reported in the short-term (at 1 week and 1 month) and maintained in the longer-term (up to 2 years). There was no significant difference in SNOT-20 score compared with FESS at any time point, except at 1 week where there was a greater (but not clinically important) reduction in favour of XprESS MSDS. The longitudinal SNOT-20 results from the observational studies were also consistent with the results from the REMODEL trial.

Comparative data were available on a number of secondary outcomes from the REMODEL trial [4] with supporting longitudinal data from the single-arm studies [6-10, 12]. In general, there were no differences reported in these outcomes between FESS and XprESS MSDS including ostia patency, subsequent rhinosinusitis episodes, work productivity and activity, complications and revision treatment. The REMODEL study did report the mean number of post-procedure debridements per patient was statistically significantly lower in the balloon arm compared to FESS (0.1 versus 1.2; $p<0.001$) [2, 4]; however, the EAC considered that this result was not generalisable to the NHS. Additionally, there was some evidence that XprESS MSDS was associated with patient benefits such as improved recovery time, reduced post discharge nasal bleeding, and reduced requirement for prescription analgesia compared with FESS [4].

There was indirect evidence reporting on the comparative efficacy of XprESS MSDS when used on different sinuses. However, subgroup analysis on a single-arm observational study showed no difference in outcomes for the type of sinus treated between maxillary, frontal and sphenoid subgroups [6].

There was no information reported in the studies on other outcomes defined in the scope, including length of hospital stay, procedure duration, rate of readmission and staff required for either procedure.

The EAC concludes that the company provided reasonable comparative evidence through the REMODEL trial that the XprESS MSDS or FinESS system provide non-inferior clinical benefits compared with FESS in selected patients with refractory CRS of RARS of the maxillary sinus with or without anterior ethmoid disease. However, uncertainty remains as to whether the procedure remains as effective for those patients indicated for surgery within the NHS, particularly those with more severe nasal polyps, as the efficacy of XprESS MSDS was not demonstrated in this group of patients. Further, the evidence on the effectiveness of treatment other than the maxillary and anterior ethmoid sinuses is very limited. Additional research is required to overcome these uncertainties. The existing evidence base is consistent with the company's claim of equivalence across health outcomes within this selected patient population.

No published economic evidence around XprESS MSDS (or its predecessor) was identified by either the company or the EAC. The company submitted a fully executable *de novo* economic model which compared XprESS MSDS with FESS and an Acclarent device (alterative balloon dilation system) which is no longer available within the NHS (see correspondence log, appendix 3). The model incorporated a decision tree followed by a Markov model structure, with a 5 year time frame. The model utilised data from the REMODEL trial, supplemented by UK specific resource use post-procedure data primarily from a national audit [15]. The national audit provided data on surgery for nasal polyposis and CRS in 87 hospitals in England and Wales during a 6-month period in 2000 (n=3,128).

The company's *de novo* model followed an appropriate clinical pathway given the data available. In its base case, XprESS MSDS was found to save £1,302 per patient versus FESS (cost per patient of £1,694 in the XprESS MSDS arm and £1,364 in the FESS arm). The company correctly identified procedure and equipment costs as key drivers of its economic analysis.

The EAC validated the company's model inputs using advice from clinical experts and pragmatic literature searching of databases and grey literature. Several model inputs were changed to values the EAC judged more plausible. In the EAC's base case, XprESS MSDS incurred costs of £330 per patient compared with FESS. This change in direction of results was driven by a reduction in the FESS procedure time based on advice the EAC received from experts and evidence in the published literature [15, 16, 72]. The EAC conducted a series of sensitivity and scenario analyses whereby the direction

of the result did not change. The model was sensitive to the duration of FESS; however, the EAC did not find plausible the duration of FESS surgery required for XprESS MSDS to become cost saving based upon the existing evidence base. XprESS was only cost saving if the majority of XprESS MSDS patients underwent surgery under local anaesthetic in an outpatient setting and all FESS patients required a follow-up hospital visit for debridement. This is not judged representative of practice within the NHS on the whole. Expert opinion on whether debridement is carried out routinely was mixed.

Hence, the EAC was unable to substantiate the company's estimated cost savings associated with XprESS MSDS. Rather, based upon the EAC's analysis using the currently available evidence base, the device probably incurs a slight cost over the 5 years. However, there remain uncertainties in key parameters used within the model, namely the duration of each procedure, length of hospital stay (including any overnight stay) and rate of revision surgery in comparable patients. Further research would be required to reduce the uncertainty and allow firmer conclusions around the cost implications of XprESS MSDS to be drawn.

Neither the company nor the EAC were able to make a comparison of the relative clinical or cost-effectiveness of XprESS MSDS with other balloon systems available within the NHS due to a paucity of data. Likewise, neither party was able to address the subgroups listed within the scope independently.

To conclude, whilst the clinical efficacy of XprESS MSDS is shown to be non-inferior to FESS in a subgroup of the patients treated within the NHS - selected patients with refractory uncomplicated CRS of RARS of the maxillary sinus with or without anterior ethmoid disease - the device may not offer cost savings within the NHS. There does, however, remain uncertainty around key parameters used within the economic model. Furthermore, patient benefits not captured within the economic analysis included a faster recovery time, less pain and less post discharge nasal bleeding with XprESS MSDS compared with FESS.

6 Implications for research

There were a number of gaps within the evidence base for XprESS MSDS leading to uncertainty within this assessment. Notably, no clinical data from the NHS on the use of XprESS were available with the evidence base consisting of US studies only. Furthermore, evidence relating to resource use was limited, with no information pertaining to the duration of surgery or length of hospital stay with XprESS MSDS.

In order to overcome the remaining uncertainties within the EAC's conclusions further evidence would need to be collected. Such a study should ideally have the following design:

- RCT of patients requiring surgery for CRS within the NHS.
- Arms comparing FESS and XprESS MSDS.
- Adequately powered with predefined outcomes and estimates of clinical effect and resource utilisation.
- Outcomes including SNOT score, procedure duration, length of stay (specifically the duration of hospital stay for day cases and the proportion needing an overnight stay), revision surgery, readmissions to hospital and subsequent acute exacerbations, with follow-up to 2 years post procedure.
- Pre-defined subgroup analysis comparing patient with polyps to those without, and to allow a comparison of efficacy on different sinuses including the maxillary, anterior ethmoid, frontal, and sphenoid sinuses.

Any other balloon systems used within the NHS at the time of the design of the study may be considered as a third arm within the study. An audit or less robust study design could be conducted in the first instance to inform resource usage and duration of surgery. This would allow the model to be re-run with less reliance on expert opinion.

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Appendix 1: Re-run company clinical evidence and adverse effects searches

Literature Search Results

The literature searches identified 395 records (Table A1.1). Following deduplication 229 records were assessed for relevance.

Table A1.1: Literature search results

Resource	Records identified
MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE	162
Embase	60
PubMed	173
TOTAL	**395**
TOTAL AFTER DEDUPLICATION	**229**

Search strategies: re-run company clinical evidence and adverse effects searches

A1.1: Source: MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1946 to Present

Interface / URL: OvidSP
Search date: 18/02/16
Retrieved records: 162
Search strategy:

1 exp Sinusitis/ or (sinusitis or rhinosinusitis).af. (23657)
2 exp Dilatation, Pathologic/ or (dilat* or balloon* or catheter* or sinuplast*).mp. (432933)
3 1 and 2 (418)
4 limit 3 to (english language and humans and yr="2006 -Current") (162)

A1.2: Source: Embase <1974 to 2016 February 17>

Interface / URL: OvidSP
Search date: 18/02/16
Retrieved records: 60
Search strategy:

1 exp sinusitis/ or exp rhinosinusitis/ (34995)
2 exp balloon catheter/ or exp balloon dilatation/ or (dilat* or balloon* or catheter*).mp. or sinuplast*.mp. (562403)
3 1 and 2 (718)

4 limit 3 to (human and english language and exclude medline journals and yr="2006 -Current") (60)

A1.3: Source: PubMed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 18/02/16
Retrieved records: 173
Search strategy:

#4 Search ("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*) AND ("Sinusitis"[Mesh] OR sinusitis OR rhinosinusitis OR sinuplast*) Filters: Publication date from 2006/01/01 to 2016/12/31; Humans; English 173
#3 Search ("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*) AND ("Sinusitis"[Mesh] OR sinusitis OR rhinosinusitis OR sinuplast*) Filters: Humans; English 274
#2 Search ("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*) AND ("Sinusitis"[Mesh] OR sinusitis OR rhinosinusitis OR sinuplast*) Filters: English 334
#1 Search ("Dilatation, Pathologic"[Mesh] OR dilat* OR balloon* OR catheter*) AND ("Sinusitis"[Mesh] OR sinusitis OR rhinosinusitis OR sinuplast*) 442

Appendix 2: EAC additional clinical evidence, adverse effects and economics searches

Literature Search Results

The searches identified 1,204 records (Table A2.1). Following within-set deduplication 698 records were assessed for relevance to the economic submission. Following within-set de-duplication, and de-duplication against the re-run company clinical evidence searches, 545 records were assessed for relevance to the clinical submission.

Table A2.1: Literature search results

Resource	Records identified
MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE	277
Embase	361
Cochrane Central Register of Controlled Trials	36
Database of Abstracts of Reviews of Effects	0
Health Technology Assessment Database	6
Cochrane Database of Systematic Reviews	2
PubMed	116
Science Citation Index Expanded (SCI-EXPANDED) / Conference Proceedings Citation Index- Science (CPCI-S)	261
Clinicaltrials.gov	86
WHO International Clinical Trials Registry Platform	50
ISRCTN registry	0
NHS Economic Evaluation Database	1
Econlit	0
Cost-Effectiveness Analysis Registry	0
Euroscan	2
Entellus Clinical Data Center Clinical Library	6
British Association of Otorhinolaryngologists, Head and Neck Surgeons (ENT UK) website	0
British Rhinological Society website	0
British Society for Allergy & Clinical Immunology website	0
Royal College of Physicians website	0
Royal College of General Practitioners website	0
Action Against Allergy (AAA) website	0
Allergy Alliance website	0
Allergy UK website	0
Asthma Relief Charity website	0
Asthma UK website	0
Asthma, Allergy and Inflammation Research Trust website	0
British Lung Foundation website	0
Fungal Infection Trust website	0
Other	0
TOTAL	**1204**
TOTAL after deduplication (within-set only)	**698**
TOTAL after deduplication (within-set, and against the re-run company clinical searches)	**545**

Note: 2 additional studies were identified through the company's submission to NICE and reviewed by the EAC.

Search strategies: EAC additional clinical evidence, adverse effects and economics searches

A2.1: Source: MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1946 to Present

Interface / URL: OvidSP

Search date: 26/02/16

Retrieved records: 277
Search strategy:

1 exp Sinusitis/ (17489)
2 Paranasal Sinus Diseases/ (4824)
3 sinusit$.ti,ab,kf. (13902)
4 (nasosinusit$ or pansinusit$ or ethmoidit$ or sphenoidit$ or antritis).ti,ab,kf. (643)
5 rhinosinusit$.ti,ab,kf. (5667)
6 ((sinus or sinuses or sinonasal or sino-nasal) adj5 (infection$1 or disease$1 or inflam$)).ti,ab,kf. (7710)
7 (RARS or CRS).ti,ab,kf. (8294)
8 (CRSwNP or CRSsNP).ti,ab,kf. (425)
9 Rhinitis/ (10106)
10 rhinit$.ti,ab,kf. (22259)
11 exp Paranasal Sinuses/ (22994)
12 ((paranasal$2 or nasal$2 or ethmoid$ or frontal$ or maxilla$ or highmore or upper jaw or sphenoid$ or ostia$) adj3 (sinus$ or cavity or cavities or antrum or antrums or mucosa$1)).ti,ab,kf. (44627)
13 (nasal adj3 (inflamm$ or virus$ or bacteri$ or infectio$)).ti,ab,kf. (2944)
14 or/1-13 (96697)
15 Dilatation/ or Dilatation, Pathologic/ (19108)
16 Catheterization/ (47577)
17 (balloon$1 or sinuplast$ or sinu-plast$).ti,ab,kf. (53089)
18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter$) adj5 dilat$).ti,ab,kf. (2151)
19 or/15-18 (108434)
20 xpress$2.ti,ab,kf. (110)
21 finess$2.ti,ab,kf. (797)
22 entellus$2.ti,ab,kf,in. (133)
23 msds.ti,ab,kf. (612)
24 or/20-23 (1652)
25 14 and 19 (680)
26 14 and 24 (4)
27 (xpress$2 multisinus or xpress$2 multi-sinus or finess$2 sinus).ti,ab,kf. (0)
28 or/25-27 (683)
29 exp animals/ not humans/ (4189142)
30 28 not 29 (648)
31 limit 30 to (english language and yr="2006 -Current") (278)
32 remove duplicates from 31 (277)

A2.2: Source: Embase 1974 to 2016 February 25

Interface / URL: OvidSP
Search date: 26/02/16
Retrieved records: 361

Search strategy:

1 exp sinusitis/ (35063)
2 paranasal sinus disease/ (3103)
3 sinusit$.ti,ab,kw. (18414)
4 (nasosinusit$ or pansinusit$ or ethmoidit$ or sphenoidit$ or antritis).ti,ab,kw. (808)
5 rhinosinusit$.ti,ab,kw. (7618)
6 ((sinus or sinuses or sinonasal or sino-nasal) adj5 (infection$1 or disease$1 or inflam$)).ti,ab,kw. (9709)
7 (RARS or CRS).ti,ab,kw. (11981)
8 (CRSwNP or CRSsNP).ti,ab,kw. (606)
9 rhinitis/ (17133)
10 rhinit$.ti,ab,kw. (32882)
11 exp paranasal sinus/ (26490)
12 ((paranasal$2 or nasal$2 or ethmoid$ or frontal$ or maxilla$ or highmore or upper jaw or sphenoid$ or ostia$) adj3 (sinus$ or cavity or cavities or antrum or antrums or mucosa$1)).ti,ab,kw. (52000)
13 (nasal adj3 (inflamm$ or virus$ or bacteri$ or infectio$)).ti,ab,kw. (3582)
14 or/1-13 (135803)
15 balloon dilatation/ (14271)
16 balloon catheter/ (13347)
17 (balloon$1 or sinuplast$ or sinu-plast$).ti,ab,kw. (78802)
18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter$) adj5 dilat$).ti,ab,kw. (2941)
19 or/15-18 (90155)
20 xpress$2.ti,ab,kw,dm,dv. (312)
21 finess$2.ti,ab,kw,dm,dv. (456)
22 entellus$2.ti,ab,kw,in,dm,dv. (156)
23 msds.ti,ab,kw. (788)
24 or/20-23 (1705)
25 14 and 19 (628)
26 14 and 24 (24)
27 (xpress$2 multisinus or xpress$2 multi-sinus or finess$2 sinus).ti,ab,kw,dm,dv. (2)
28 or/25-27 (638)
29 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5296414)
30 28 not 29 (619)
31 limit 30 to (english language and yr="2006 -Current") (379)
32 remove duplicates from 31 (361)

A2.3: Source: Database of Abstracts of Reviews of Effects: Issue 2 of 4, April 2015

Interface / URL: Cochrane Library / Wiley

Search date: 26/02/16
Retrieved records: 0
Search strategy:

#1 [mh Sinusitis] 814
#2 [mh ^"Paranasal Sinus Diseases"] 54
#3 (sinusit*) 2127
#4 (nasosinusit* or pansinusit* or ethmoidit* or sphenoidit* or antritis) 43
#5 (rhinosinusit*) 776
#6 ((sinus or sinuses or sinonasal or sino-nasal) near/5 (infection* or disease* or inflam*)) 676
#7 (RARS or CRS) 738
#8 (CRSwNP or CRSsNP) 41
#9 [mh ^Rhinitis] 718
#10 (rhinit*) 7743
#11 [mh "Paranasal Sinuses"] 429
#12 ((paranasal* or nasal* or ethmoid* or frontal* or maxilla* or highmore or "upper jaw" or sphenoid* or ostia*) near/3 (sinus* or cavity or cavities or antrum or antrums or mucosa*)) 3001
#13 (nasal near/3 (inflamm* or virus* or bacteri* or infectio*)) 411
#14 [51-#13] 12233
#15 [mh ^Dilatation] or [mh ^"Dilatation, Pathologic"] 513
#16 [mh ^Catheterization] 1572
#17 (balloon* or sinuplast* or sinu-plast*) 7775
#18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter*) near/5 dilat*) 155
#19 [52-#18][51-#18] 9412
#20 (xpress*) 13
#21 (finess*) 24
#22 (entellus*) 6
#23 (msds) 43
#24 {or #20-#23} 86
#25 #14 and #19 85
#26 #14 and #24 6
#27 (xpress* next multisinus or xpress* next multi-sinus or finess* next sinus) 0
#28 {or #25-#27} 91
#29 #28 Publication Year from 2006 to 2016 64
#30 #29 in Other Reviews 0

A2.4: Source: Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2016

Interface / URL: Cochrane Library / Wiley
Search date: 26/02/16
Retrieved records: 36
Search strategy:

#1 [mh Sinusitis] 814
#2 [mh ^"Paranasal Sinus Diseases"] 54
#3 (sinusit*) 2127
#4 (nasosinusit* or pansinusit* or ethmoidit* or sphenoidit* or antritis) 43
#5 (rhinosinusit*) 776
#6 ((sinus or sinuses or sinonasal or sino-nasal) near/5 (infection* or disease* or inflam*)) 676
#7 (RARS or CRS) 738
#8 (CRSwNP or CRSsNP) 41
#9 [mh ^Rhinitis] 718
#10 (rhinit*) 7743
#11 [mh "Paranasal Sinuses"] 429
#12 ((paranasal* or nasal* or ethmoid* or frontal* or maxilla* or highmore or "upper jaw" or sphenoid* or ostia*) near/3 (sinus* or cavity or cavities or antrum or antrums or mucosa*)) 3001
#13 (nasal near/3 (inflamm* or virus* or bacteri* or infectio*)) 411
#14 [51-#13] 12233
#15 [mh ^Dilatation] or [mh ^"Dilatation, Pathologic"] 513
#16 [mh ^Catheterization] 1572
#17 (balloon* or sinuplast* or sinu-plast*) 7775
#18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter*) near/5 dilat*) 155
#19 [52-#18][51-#18] 9412
#20 (xpress*) 13
#21 (finess*) 24
#22 (entellus*) 6
#23 (msds) 43
#24 {or #20-#23} 86
#25 #14 and #19 85
#26 #14 and #24 6
#27 (xpress* next multisinus or xpress* next multi-sinus or finess* next sinus) 0
#28 {or #25-#27} 91
#29 #28 Publication Year from 2006 to 2016 64
#30 #29 in Other Reviews 0
#31 #29 in Trials 36

A2.5: Source: Health Technology Assessment Database: Issue 1 of 4, January 2016

Interface / URL: Cochrane Library / Wiley
Search date: 26/02/16
Retrieved records: 6
Search strategy:

#1 [mh Sinusitis] 814

#2 [mh ^"Paranasal Sinus Diseases"] 54
#3 (sinusit*) 2127
#4 (nasosinusit* or pansinusit* or ethmoidit* or sphenoidit* or antritis) 43
#5 (rhinosinusit*) 776
#6 ((sinus or sinuses or sinonasal or sino-nasal) near/5 (infection* or disease* or inflam*)) 676
#7 (RARS or CRS) 738
#8 (CRSwNP or CRSsNP) 41
#9 [mh ^Rhinitis] 718
#10 (rhinit*) 7743
#11 [mh "Paranasal Sinuses"] 429
#12 ((paranasal* or nasal* or ethmoid* or frontal* or maxilla* or highmore or "upper jaw" or sphenoid* or ostia*) near/3 (sinus* or cavity or cavities or antrum or antrums or mucosa*)) 3001
#13 (nasal near/3 (inflamm* or virus* or bacteri* or infectio*)) 411
#14 [51-#13] 12233
#15 [mh ^Dilatation] or [mh ^"Dilatation, Pathologic"] 513
#16 [mh ^Catheterization] 1572
#17 (balloon* or sinuplast* or sinu-plast*) 7775
#18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter*) near/5 dilat*) 155
#19 [52-#18] 9412
#20 (xpress*) 13
#21 (finess*) 24
#22 (entellus*) 6
#23 (msds) 43
#24 {or #20-#23} 86
#25 #14 and #19 85
#26 #14 and #24 6
#27 (xpress* next multisinus or xpress* next multi-sinus or finess* next sinus) 0
#28 {or #25-#27} 91
#29 #28 Publication Year from 2006 to 2016 64
#30 #29 in Other Reviews 0
#31 #29 in Trials 36
#32 #29 in Technology Assessments 6

A2.6: Source: NHS Economic Evaluation Database: Issue 2 of 4, April 2015

Interface / URL: Cochrane Library / Wiley
Search date: 26/02/16
Retrieved records: 1
Search strategy:

#1 [mh Sinusitis] 814
#2 [mh ^"Paranasal Sinus Diseases"] 54
#3 (sinusit*) 2127

#4 (nasosinusit* or pansinusit* or ethmoidit* or sphenoidit* or antritis) 43
#5 (rhinosinusit*) 776
#6 ((sinus or sinuses or sinonasal or sino-nasal) near/5 (infection* or disease* or inflam*)) 676
#7 (RARS or CRS) 738
#8 (CRSwNP or CRSsNP) 41
#9 [mh ^Rhinitis] 718
#10 (rhinit*) 7743
#11 [mh "Paranasal Sinuses"] 429
#12 ((paranasal* or nasal* or ethmoid* or frontal* or maxilla* or highmore or "upper jaw" or sphenoid* or ostia*) near/3 (sinus* or cavity or cavities or antrum or antrums or mucosa*)) 3001
#13 (nasal near/3 (inflamm* or virus* or bacteri* or infectio*)) 411
#14 [51-#13] 12233
#15 [mh ^Dilatation] or [mh ^"Dilatation, Pathologic"] 513
#16 [mh ^Catheterization] 1572
#17 (balloon* or sinuplast* or sinu-plast*) 7775
#18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter*) near/5 dilat*) 155
#19 [52-#18] 9412
#20 (xpress*) 13
#21 (finess*) 24
#22 (entellus*) 6
#23 (msds) 43
#24 {or #20-#23} 86
#25 #14 and #19 85
#26 #14 and #24 6
#27 (xpress* next multisinus or xpress* next multi-sinus or finess* next sinus) 0
#28 {or #25-#27} 91
#29 #28 Publication Year from 2006 to 2016 64
#30 #29 in Other Reviews 0
#31 #29 in Trials 36
#32 #29 in Technology Assessments 6
#33 #29 in Economic Evaluations 1

A2.7: Source: Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2016

Interface / URL: Cochrane Library / Wiley
Search date: 26/02/16
Retrieved records: 2
Search strategy:

#1 [mh Sinusitis] 814
#2 [mh ^"Paranasal Sinus Diseases"] 54
#3 (sinusit*):ti,ab,kw 1910

#4 (nasosinusit* or pansinusit* or ethmoidit* or sphenoidit* or antritis):ti,ab,kw 12
#5 (rhinosinusit*):ti,ab,kw 721
#6 ((sinus or sinuses or sinonasal or sino-nasal) near/5 (infection* or disease* or inflam*)):ti,ab,kw 561
#7 (RARS or CRS):ti,ab,kw 573
#8 (CRSwNP or CRSsNP):ti,ab,kw 28
#9 [mh ^Rhinitis] 718
#10 (rhinit*):ti,ab,kw 7453
#11 [mh "Paranasal Sinuses"] 429
#12 ((paranasal* or nasal* or ethmoid* or frontal* or maxilla* or highmore or "upper jaw" or sphenoid* or ostia*) near/3 (sinus* or cavity or cavities or antrum or antrums or mucosa*)):ti,ab,kw 2872
#13 (nasal near/3 (inflamm* or virus* or bacteri* or infectio*)):ti,ab,kw 346
#14 [51-#13] 11562
#15 [mh ^Dilatation] or [mh ^"Dilatation, Pathologic"] 513
#16 [mh ^Catheterization] 1572
#17 (balloon* or sinuplast* or sinu-plast*):ti,ab,kw 7354
#18 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter*) near/5 dilat*):ti,ab,kw 132
#19 [52-#18] 8994
#20 (xpress*):ti,ab,kw 9
#21 (finess*):ti,ab,kw 19
#22 (entellus*):ti,ab,kw 0
#23 (msds):ti,ab,kw 38
#24 {or #20-#23} 66
#25 #14 and #19 71
#26 #14 and #24 0
#27 (xpress* next multisinus or xpress* next multi-sinus or finess* next sinus):ti,ab,kw 0
#28 {or #25-#27} 71
#29 #28 Publication Year from 2006 to 2016 45
#30 #29 in Cochrane Reviews (Reviews and Protocols) 2

A2.8: Source: Science Citation Index Expanded (SCI-EXPANDED) / Conference Proceedings Citation Index- Science (CPCI-S)

Interface / URL: Web of Science
Search date: 28/02/16
Retrieved records: 261
Search strategy:

All lines: Indexes=SCI-EXPANDED, CPCI-S

23 261 (#22) AND LANGUAGE: (English) Timespan=2006-2016

22 411 #21 OR #20 OR #19

21 0 TS=("xpress* multisinus" or "xpress* multi-sinus" or "finess* sinus")

20 7 #10 and #18

19 405 #10 and #13

18 4,216 #17 OR #16 OR #15 OR #14

17 753 TS=("msds")

16 451 TS=(entellus*)

15 2,735 TS=(finess*)

14 277 TS=(xpress*)

13 74,332 #12 OR #11

12 2,003 TS=(("sinus" or "multisinus" or "sinuses" or "sinonasal" or "sino-nasal" or catheter*) near/5 dilat*)

11 73,242 TS=(balloon* or sinuplast* or "sinu-plast*")

10 78,172 #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

9 4,176 TS=("nasal" near/3 (inflamm* or virus* or bacteri* or infectio*))

8 34,358 TS=((paranasal* or nasal* or ethmoid* or frontal* or maxilla* or "highmore" or "upper jaw" or sphenoid* or ostia*) near/3 (sinus* or "cavity" or "cavities" or "antrum" or "antrums" or mucosa*))

7 24,690 TS=(rhinit*)

6 359 TS=("CRSwNP" or "CRSsNP")

5 9,895 TS=("RARS" or "CRS")

4 6,962 TS=(("sinus" or "sinuses" or "sinonasal" or "sino-nasal") near/5 (infection* or disease* or inflam*))

3 6,630 TS=(rhinosinusit*)

2 358 TS=(nasosinusit* or pansinusit* or ethmoidit* or sphenoidit* or "antritis")

1 12,170 TS=(sinusit*)

A2.9: Source: PubMed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 29/02/16
Retrieved records: 116
Search strategy:

#34 Search (#32 NOT #33) 116
#33 Search medline[sb] 22995907
#32 Search (#28 NOT #29) Filters: Publication date from 2006/01/01 to 2016/12/31; English 730
#31 Search (#28 NOT #29) Filters: English 1438
#30 Search (#28 NOT #29) 1845
#29 Search (animals[mh] NOT humans[mh:noexp]) 4181678
#28 Search (#25 OR #26 OR #27) 1952
#27 Search (xpress*[tiab] AND (multisinus[tiab] OR multi-sinus[tiab])) OR (finess*[tiab] AND sinus[tiab]) 1
#26 Search (#14 AND #24) 5
#25 Search (#14 AND #19) 1949
#24 Search (#20 OR #21 OR #22 OR #23) 1694
#23 Search msds[tiab] 615
#22 Search (entellus*[tiab] OR entellus*[ad]) 134
#21 Search finess*[tiab] 822
#20 Search xpress*[tiab] 123
#19 Search (#15 OR #16 OR #17 OR #18) 117391
#18 Search ((sinus[tiab] OR multisinus[tiab] OR sinuses[tiab] OR sinonasal[tiab] OR sino-nasal[tiab] OR catheter*[tiab]) AND dilat*[tiab]) 9721
#17 Search (balloon*[tiab] OR sinuplast*[tiab] OR sinu-plast*[tiab]) 57138
#16 Search "Catheterization"[mh:noexp] 47529
#15 Search "Dilatation"[mh:noexp] OR "Dilatation, Pathologic"[mh:noexp] 19086
#14 Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) 128794
#13 Search (nasal[tiab] AND (inflamm*[tiab] OR virus*[tiab] OR bacteri*[tiab] OR infectio*[tiab])) 20504
#12 Search ((paranasal*[tiab] OR nasal*[tiab] OR ethmoid*[tiab] OR frontal*[tiab] OR maxilla*[tiab] OR highmore[tiab] OR upper jaw[tiab] OR sphenoid*[tiab] OR ostia*[tiab]) AND (sinus*[tiab] OR cavity[tiab] OR cavities[tiab] OR antrum[tiab] OR antrums[tiab] OR mucosa*[tiab])) 56907
#11 Search "Paranasal Sinuses"[mh] 22980
#10 Search rhinit*[tiab] 22495

#9 Search "Rhinitis"[mh:noexp] 10097
#8 Search (CRSwNP[tiab] OR CRSsNP[tiab]) 447
#7 Search (RARS[tiab] OR CRS[tiab]) 8396
#6 Search ((sinus[tiab] OR sinuses[tiab] OR sinonasal[tiab] OR sino-nasal[tiab]) AND (infection*[tiab] OR disease*[tiab] OR inflam*[tiab])) 28693
#5 Search rhinosinusit*[tiab] 5814
#4 Search (nasosinusit*[tiab] OR pansinusit*[tiab] OR ethmoidit*[tiab] OR sphenoidit*[tiab] OR antritis[tiab]) 648
#3 Search sinusit*[tiab] 14030
#2 Search "Paranasal Sinus Diseases"[mh:noexp] 4823
#1 Search "Sinusitis"[mh] 17466

A2.10: Source: ClinicalTrials.gov
Interface / URL: https://clinicaltrials.gov/ct2/home
Search date: 29/02/16
Retrieved records: 86
Search strategy:

The following 9 searches were carried out separately, using the expert interface available at: https://www.clinicaltrials.gov/ct2/results/refine?show_xprt=Y.

219 results were downloaded separately and imported into an EndNote Library. EndNote default de-duplication settings were applied. 133 records were excluded as duplicates, with 86 records retrieved.

1. ((sinusitis OR sinusitides OR nasosinusitis OR nasosinusitides OR pansinusitis OR pansinusitides OR ethmoiditis OR sphenoiditis OR antritis OR rhinosinusitis OR rhinosinusitides OR RARS OR CRS OR CRSwNP OR CRSsNP OR rhinitis) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 26 studies

2. ((sinusitis OR sinusitides OR nasosinusitis OR nasosinusitides OR pansinusitis OR pansinusitides OR ethmoiditis OR sphenoiditis OR antritis OR rhinosinusitis OR rhinosinusitides OR RARS OR CRS OR CRSwNP OR CRSsNP OR rhinitis) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 22 studies

3. ((sinus OR sinuses OR sinonasal OR "sino-nasal") AND (infection OR infections OR disease OR diseases OR inflamed OR inflammatory OR inflammation OR inflammations) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 27 studies

4. ((sinus OR sinuses OR sinonasal OR "sino-nasal") AND (infection OR infections OR disease OR diseases OR inflamed OR inflammatory OR inflammation OR inflammations) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 29 studies

5. ((paranasal OR nasal OR ethmoid OR ethmoidal OR frontal OR maxillary OR highmore OR "upper jaw" OR sphenoid OR sphenoidal OR ostia OR ostial) AND (sinus OR sinuses OR cavity OR cavities OR antrum OR antrums OR mucosa OR mucosas OR mucosal) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 28 studies

6. ((paranasal OR nasal OR ethmoid OR ethmoidal OR frontal OR maxillary OR highmore OR "upper jaw" OR sphenoid OR sphenoidal OR ostia OR ostial) AND (sinus OR sinuses OR cavity OR cavities OR antrum OR antrums OR mucosa OR mucosas OR mucosal) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 27 studies

7. ((nasal AND (inflamed OR inflammatory OR inflammation OR inflammations OR virus OR viruses OR bacteria OR bacterias OR bacterial OR bacterium OR infection OR infections OR infectious)) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 25 studies

8. ((nasal AND (inflamed OR inflammation OR inflammatory OR inflammation OR inflammations OR virus OR viruses OR bacteria OR bacterias OR bacterial OR bacterium OR infection OR infections OR infectious)) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 25 studies

9. (xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm) AND (sinus OR multisinus) = 10 studies

A2.11: Source: International Clinical Trials Registry Platform
Interface / URL: http://apps.who.int/trialsearch/Default.aspx
Search date: 01/03/16
Retrieved records: 50
Search strategy:

The following 9 searches were carried out separately, using the search interface at: http://apps.who.int/trialsearch/Default.aspx

94 results were downloaded separately and imported into an EndNote Library. EndNote default de-duplication settings were applied. 44 records were excluded as duplicates, with 50 records retrieved.

1. sinus* AND balloon* OR nasosinus* AND balloon* OR pansinus* AND balloon* OR ethmoidit* AND balloon* OR sphenoidit* AND balloon* OR antritis AND balloon* OR rhinosinus* AND balloon* OR RARS AND balloon* OR CRS AND balloon* OR CRSwNP AND balloon* OR CRSsNP AND balloon* OR rhinit* AND balloon* OR sinonasal AND balloon* OR nasal AND balloon* = 28 (28 records for 28 trials)

2. sinus* AND sinuplast* OR nasosinus* AND sinuplast* OR pansinus* AND sinuplast* OR ethmoidit* AND sinuplast* OR sphenoidit* AND sinuplast* OR antritis AND sinuplast* OR rhinosinus* AND sinuplast* OR RARS AND sinuplast* OR CRS AND sinuplast* OR CRSwNP AND sinuplast* OR CRSsNP AND sinuplast* OR rhinit* AND sinuplast* OR sinonasal AND sinuplast* OR nasal AND sinuplast* = 8 (8 records for 8 trials)

3. sinus* AND sinu-plast* OR nasosinus* AND sinu-plast* OR pansinus* AND sinu-plast* OR ethmoidit* AND sinu-plast* OR sphenoidit* AND sinu-plast* OR antritis AND sinu-plast* OR rhinosinus* AND sinu-plast* OR RARS AND sinu-plast* OR CRS AND sinu-plast* OR CRSwNP AND sinu-plast* OR CRSsNP AND sinu-plast* OR rhinit* AND sinu-plast* OR sinonasal AND sinu-plast* OR nasal AND sinu-plast* = 8 (8 records for 8 trials)

4. sinus* AND xpress* OR nasosinus* AND xpress* OR pansinus* AND xpress* OR ethmoidit* AND xpress* OR sphenoidit* AND xpress* OR antritis AND xpress* OR rhinosinus* AND xpress* OR RARS AND xpress* OR CRS AND xpress* OR CRSwNP AND xpress* OR CRSsNP AND xpress* OR rhinit* AND xpress* OR sinonasal AND xpress* OR nasal AND xpress* = 4 (4 records for 4 trials)

5. sinus* AND finess* OR nasosinus* AND finess* OR pansinus* AND finess* OR ethmoidit* AND finess* OR sphenoidit* AND finess* OR antritis AND finess* OR rhinosinus* AND finess* OR RARS AND finess* OR CRS AND finess* OR CRSwNP AND finess* OR CRSsNP AND finess* OR rhinit* AND finess* OR sinonasal AND finess* OR nasal AND finess* = 4 (4 records for 4 trials)

6. sinus* AND entellus* OR nasosinus* AND entellus* OR pansinus* AND entellus* OR ethmoidit* AND entellus* OR sphenoidit* AND entellus* OR antritis AND entellus* OR rhinosinus* AND entellus* OR RARS AND entellus* OR CRS AND entellus* OR CRSwNP AND entellus* OR CRSsNP AND entellus* OR rhinit* AND entellus* OR sinonasal AND entellus* OR nasal AND entellus* = 9 (9 records for 9 trials)

7. sinus* AND msds OR nasosinus* AND msds OR pansinus* AND msds OR ethmoidit* AND msds OR sphenoidit* AND msds OR antritis AND msds OR rhinosinus* AND msds OR RARS AND msds OR CRS AND msds OR CRSwNP AND msds OR CRSsNP AND msds OR rhinit* AND msds OR sinonasal AND msds OR nasal AND msds = 0 results

8. sinus* AND dilat* OR nasosinus* AND dilat* OR pansinus* AND dilat* OR ethmoidit* AND dilat* OR sphenoidit* AND dilat* OR antritis AND dilat* OR rhinosinus* AND dilat* OR RARS AND dilat* OR CRS AND dilat* OR CRSwNP AND dilat* OR CRSsNP AND dilat* OR rhinit* AND dilat* OR sinonasal AND dilat* OR nasal AND dilat* = 33 (33 records for 33 trials)

9. xpress* AND multisinus = 0 results

A2.12: Source: ISRCTN registry
Interface / URL: http://www.isrctn.com/
Search date: 01/03/16
Retrieved records: 0
Search strategy:

The following 9 searches were carried out separately, using the homepage search interface. 0 results were retrieved.

1. ((sinusitis OR sinusitides OR nasosinusitis OR nasosinusitides OR pansinusitis OR pansinusitides OR ethmoiditis OR sphenoiditis OR antritis OR rhinosinusitis OR rhinosinusitides OR RARS OR CRS OR CRSwNP OR CRSsNP OR rhinitis) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 0 results

2. ((sinusitis OR sinusitides OR nasosinusitis OR nasosinusitides OR pansinusitis OR pansinusitides OR ethmoiditis OR sphenoiditis OR antritis OR rhinosinusitis OR rhinosinusitides OR RARS OR CRS OR CRSwNP OR CRSsNP OR rhinitis) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 0 results

3. ((sinus OR sinuses OR sinonasal OR "sino-nasal") AND (infection OR infections OR disease OR diseases OR inflamed OR inflammatory OR inflammation OR inflammations) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 0 (2 results returned; assessed online by the information specialist and excluded as irrelevant)

4. ((sinus OR sinuses OR sinonasal OR "sino-nasal") AND (infection OR infections OR disease OR diseases OR inflamed OR inflammatory OR inflammation OR inflammations) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 0 (6 results returned; assessed online by the information specialist and excluded as irrelevant)

5. ((paranasal OR nasal OR ethmoid OR ethmoidal OR frontal OR maxillary OR highmore OR "upper jaw" OR sphenoid OR sphenoidal OR ostia OR ostial) AND (sinus OR sinuses OR cavity OR cavities OR antrum OR antrums OR mucosa OR mucosas OR mucosal) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 0 results

6. ((paranasal OR nasal OR ethmoid OR ethmoidal OR frontal OR maxillary OR highmore OR "upper jaw" OR sphenoid OR sphenoidal OR ostia OR ostial) AND (sinus OR sinuses OR cavity OR cavities OR antrum OR antrums OR mucosa OR mucosas OR mucosal) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 0 (2 results returned; assessed online by the information specialist and excluded as irrelevant)

7. ((nasal AND (inflamed OR inflammatory OR inflammation OR inflammations OR virus OR viruses OR bacteria OR bacterias OR bacterial OR bacterium OR infection OR infections OR infectious)) AND (balloon OR balloons OR sinuplasty OR sinuplasties OR "sinu-plasty" OR "sinu-plasties" OR xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm OR entellus OR entellusr OR entellustm OR msds)) = 0 (3 results returned; assessed online by the information specialist and excluded as irrelevant)

8. ((nasal AND (inflamed OR inflammation OR inflammatory OR inflammation OR inflammations OR virus OR viruses OR bacteria OR bacterias OR bacterial OR bacterium OR infection OR infections OR infectious)) AND (dilate OR dilates OR dilated OR dilating OR dilation OR dilations OR dilator OR dilators OR dilatory OR dilatate OR dilatates OR dilatated OR dilatating OR dilatation OR dilatations OR dilatator OR dilatators OR dilatatory)) = 0 (3 results returned; assessed online by the information specialist and excluded as irrelevant)

9. (xpress OR xpressr OR xpresstm OR finess OR finessr OR finesstm) AND (sinus OR multisinus) = 0 results

A2.13: Source: Econlit 1886 to January 2016
Interface / URL: OvidSP

Search date: 01/03/16
Retrieved records: 0
Search strategy:

1 sinusit$.af. 4
2 (nasosinusit$ or pansinusit$ or ethmoidit$ or sphenoidit$ or antritis).af. 0
3 rhinosinusit$.af. 0
4 ((sinus or sinuses or sinonasal or sino-nasal) adj5 (infection$1 or disease$1 or inflam$)).af. 0
5 (RARS or CRS).af. 134
6 (CRSwNP or CRSsNP).af. 0
7 rhinit$.af. 10
8 ((paranasal$2 or nasal$2 or ethmoid$ or frontal$ or maxilla$ or highmore or upper jaw or sphenoid$ or ostia$) adj3 (sinus$ or cavity or cavities or antrum or antrums or mucosa$1)).af. 1
9 (nasal adj3 (inflamm$ or virus$ or bacteri$ or infectio$)).af. 0
10 or/1-9 148
11 (balloon$1 or sinuplast$ or sinu-plast$).af. 50
12 ((sinus or multisinus or sinuses or sinonasal or sino-nasal or catheter$) adj5 dilat$).af. 0
13 xpress$2.af. 7
14 finess$2.af. 36
15 entellus$2.af. 0
16 msds.af. 1
17 or/11-16 94
18 10 and 17 0
19 (xpress$2 multisinus or xpress$2 multi-sinus or finess$2 sinus).af. 0
20 18 or 19 0

A2.14: Source: EuroScan
Interface / URL: https://www.euroscan.org/
Search date: 01/03/16
Retrieved records: 2
Search strategy:

Search interface used at: https://www.euroscan.org/search

The following terms were searched on separately. Results were assessed online by the information specialist for relevance. Only search results returned under the headings ‘Devices’, ‘Procedures’ or ‘Other’ were assessed. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

sinusitis = 2 retrieved (6 returned and assessed)
sinusitides = 0

nasosinusitis = 0
nasosinusitides = 0
pansinusitis = 0
pansinusitides = 0
ethmoiditis = 0
sphenoiditis = 0
antritis = 0
rhinosinusitis = 0 (2 returned and assessed)
rhinosinusitides = 0
RARS = 0
CRS = 0 (3 returned and assessed)
CRSwNP = 0
CRSsNP = 0
rhinitis = 0 (2 returned and assessed)
sinus = 0 (34 returned and assessed)
sinuses = 0 (4 returned and assessed)
sinonasal = 0 (3 returned and assessed)
paranasal = 0 (1 returned and assessed)
nasal = 0 (24 returned and assessed)
ethmoid = 0 (2 returned and assessed)
ethmoidal = 0 (1 returned and assessed)
frontal = 0 (8 returned and assessed)
maxillary = 0 (5 returned and assessed)
highmore = 0
jaw = 0 (8 returned and assessed)
sphenoid = 0 (3 returned and assessed)
sphenoidal = 0 (1 returned and assessed)
ostia = 0 (3 returned and assessed)
ostial = 0 (5 returned and assessed)

A2.15: Source: Cost-Effectiveness Analysis (CEA) Registry
Interface / URL: https://research.tufts-nemc.org/cear4/Home.aspx
Search date: 01/03/16
Retrieved records: 0
Search strategy:

The basic search interface was used at the above url. The following terms were searched on separately. Results were assessed online by the information specialist for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found, published from 2006 to date, were retrieved.

sinusitis = 0 (5 returned and assessed)
sinusitides = 0
nasosinusitis = 0
nasosinusitides = 0

pansinusitis = 0
pansinusitides = 0
ethmoiditis = 0
sphenoiditis = 0
antritis = 0
rhinosinusitis = 0 (2 returned and assessed)
rhinosinusitides = 0
RARS = 0
CRS = 0 (3)
CRSwNP = 0
CRSsNP = 0
rhinitis = 0 (9 returned and assessed)
sinus = 0 (18 returned and assessed)
sinuses = 0
sinonasal = 0
paranasal = 0
nasal = 0 (14 returned and assessed)
ethmoid = 0 (1 returned and assessed)
ethmoidal = 0
frontal = 0 (1)
maxillary = 0 (2 returned and assessed)
highmore = 0
jaw = 0 (3 returned and assessed)
sphenoid = 0
sphenoidal = 0
ostia = 0
ostial = 0

A2.16: Source: Entellus Clinical Data Center Clinical Library
Interface / URL: http://knowledge.entellusmedical.com/clinical-data/clinical-library
Search date: 01/03/16
Retrieved records: 6
Search strategy:

All citations listed at the URL above were checked against the EndNote library of records already retrieved from other search sources. Any citations not already found were retrieved.

A2.17: Source: British Rhinological Society website
Interface/URL: http://www.britishrhinologicalsociety.org.uk/
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

The website had no search functionality so Google Advanced Search (https://www.google.com/advanced_search) was used to search across the website. The website url was entered into the 'site or domain' search box, then each of the following terms was searched on individually using 'all these words' search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

A2.18: Source: British Society for Allergy & Clinical Immunology website
Interface/URL: www.bsaci.org/
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

Each of the following terms was searched on individually using the homepage search box. Some content on this site is held in a secure zone, only accessible to members. Returned results which were freely accessible were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties

sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

A2.19: Source: Royal College of Physicians website
Interface/URL: https://www.rcplondon.ac.uk/
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

Each of the following terms was searched on individually using the homepage search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus

entellusr
entellustm
msds

A2.20: Source: Royal College of General Practitioners website
Interface/URL: http://www.rcgp.org.uk/
Search date: 02/03/2016 and 03/03/2016
Retrieved records: 0
Search strategy:

Each of the following terms was searched on individually using the homepage search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

A2.21: Source: Action Against Allergy (AAA) website
Interface/URL: www.actionagainstallergy.co.uk
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

The website had no search functionality so Google Advanced Search (https://www.google.com/advanced_search) was used to search across the website. The website url was entered into the 'site or domain' search box, then each of the

following terms was searched on individually using ‘all these words’ search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

A2.22: Source: Allergy UK
Interface/URL: www.allergyuk.org
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

Each of the following terms was searched on individually using the homepage search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations

dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

A2.23: Source: Allergy Alliance website
Interface/URL: http://www.allergyalliance.org/index.html
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

It was not possible to access the above URL, therefore no search was conducted on this resource. Access was attempted in more than1 browser, but on each occasion a message was returned indicating that the website was not available. The URL used was the same as that provided at the following:
http://www.fabresearch.org/viewItem.php?id=8628.

A2.24: Source: Asthma Relief Charity Website
Interface/URL: http://www.asthmarelief.org.uk/
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

The website had no search functionality so Google Advanced Search (https://www.google.com/advanced_search) was used to search across the website. The website url was entered into the 'site or domain' search box, then each of the following terms was searched on individually using 'all these words' search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties

dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

A2.25: Source: Asthma UK website
Interface/URL: www.asthma.org.uk
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

The website had no search functionality so Google Advanced Search (https://www.google.com/advanced_search) was used to search across the website. The website url was entered into the 'site or domain' search box, then each of the following terms was searched on individually using 'all these words' search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm

entellus
entellusr
entellustm
msds

A2.26: Source: Asthma, Allergy and Inflammation Research Trust website
Interface/URL: http://www.aaircharity.org
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

Each of the following searches was conducted individually using the search box on the 'Information for Researchers Page' within the Our Research drop down menu. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon or balloons
sinuplasty or sinuplasties
sinu-plasty or sinu-plasties
dilation or dilations
dilatation or dilatations
xpress or xpressr or xpresstm
finess or finessr or finesstm
entellus or entellusr or entellustm
msds

A2.27: Source: British Lung Foundation website
Interface/URL: www.blf.org.uk
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

Each of the following searches was conducted individually using the homepage search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon or balloons
sinuplasty or sinuplasties
sinu-plasty or sinu-plasties
dilation or dilations
dilatation or dilatations
xpress or xpressr or xpresstm
finess or finessr or finesstm

entellus or entellusr or entellustm
msds

A2.28: Source: Fungal Infection Trust website
Interface/URL: http://www.fungalinfectiontrust.org
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

The website had no search functionality so Google Advanced Search (https://www.google.com/advanced_search) was used to search across the website. The website url was entered into the 'site or domain' search box, then each of the following terms was searched on individually using 'all these words' search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

A2.29: Source: British Association of Otorhinolaryngologists, Head and Neck Surgeons (ENT UK) website
Interface/URL:
Search date: 02/03/2016
Retrieved records: 0
Search strategy:

Each of the following terms was searched on individually using the homepage search box. Returned results were assessed online by the searcher for relevance. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

balloon
balloons
sinuplasty
sinuplasties
sinu-plasty
sinu-plasties
dilation
dilations
dilatation
dilatations
xpress
xpressr
xpresstm
finess
finessr
finesstm
entellus
entellusr
entellustm
msds

Appendix 3: Re-run company economics searches

Literature Search Results

The literature searches identified 90 records (Table A3.1). Following deduplication 55 records were assessed for relevance.

Table A3.1: Literature search results

Resource	Records identified
MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE	19
Embase	49
PubMed	22
TOTAL	**90**
TOTAL AFTER DEDUPLICATION	**55**

Search strategies: re-run company economics searches

A.3.1: Source: MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE <1946 to Present>

Interface / URL: OvidSP
Search date: 09/03/16
Retrieved records: 19
Search strategy:

1 exp Sinusitis/ or (sinusitis or rhinosinusitis or rhino-sinusitis).mp. (23698)
2 exp dilatation, pathologic/ or (dilat* or balloon* or catheter*).mp. (433899)
3 sinuplast*.mp. (71)
4 (1 and 2) or 3 (436)
5 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. (1112103)
6 4 and 5 (26)
7 limit 6 to (english language and yr="2010 -Current") (19)

A.3.2: Source: Embase <1974 to 2016 March 08>

Interface / URL: OvidSP
Search date: 09/03/16
Retrieved records: 49
Search strategy:

1 exp sinusitis/ or exp rhinosinusitis/ (35224)
2 exp balloon catheter/ or exp balloon dilatation/ or (dilat* or balloon* or catheter*).mp. (564310)

3 sinuplast*.mp. (117)
4 (1 and 2) or 3 (754)
5 (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. (4521555)
6 4 and 5 (91)
7 limit 6 to (english language and yr="2010 -Current") (49)

A.3: Source: PubMed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 09/03/16
Retrieved records: 22
Search strategy:

#3 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*) Filters: Publication date from 2010/01/01 to 2016/12/31; English 22
#2 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*) Filters: Publication date from 2010/01/01 to 2016/12/31 23
#1 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*) 49

Appendix 4: EAC cost-effectiveness review excluded studies

Study	Primary reason for exclusion at full paper review
Chandra *et al.* (2016) [4]	Nothing on costs
Levy *et al.* (2016) [91]	Nothing on costs
Bizaki *et al.* (2014) [92]	Nothing on costs
Ference *et al.* (2014) [66]	Intervention is hybrid surgery and not specifically using XprESS MSDS
Ference *et al.* (2015) [65]	Intervention is hybrid surgery and not specifically using XprESS MSDS
Bikhazi *et al.* (2014) [3]	Nothing on costs
Cutler *et al.* (2013) [2]	Nothing on costs
BlueCross BlueShield (2013) [93]	Nothing on costs
Koskinen *et al.* (2012) [94]	Nothing on costs
Plaza *et al.* (2011) [95]	Nothing on costs
Ramadan *et al.* (2010) [96]	Nothing on costs
Friedman *et al.* (2008a) [71]	Intervention is not XprESS (other balloon system)
Koskinen *et al.* (2016) [94]	Intervention is not XprESS (other balloon system)
Bizaki *et al.* (2015) [97]	Nothing on costs
BlueCross BlueShield (2012) [98]	Duplicate of BlueCross BlueShield (2013) – abstract
Safety Australian (2016) [99]	Review - no cost-effectiveness studies identified
NCT02278484	Single arm study, no cost data
NCT01612780	Single arm study, no cost data
NCT01115309	Single arm study, no cost data
NCT00986830	Single arm study, no cost data
NCT01525862	Single arm study, no cost data
NCT00849953	Single arm study, no cost data
NCT01525849	Nothing on costs
NCT01319305	Single arm study, no cost data
HealthPACT (2014) [100]	Review - no cost-effectiveness studies identified
Friedman *et al.* (2008b) [101]	Duplicate of Friedman *et al.* (2008a)

Appendix 5: Quality assessment of company's *de novo* economic model

Study question	Response (Yes/No/Not clear/NA)	EAC 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?	Not clear	Although a rationale was not explicitly stated, the comparators matched those in NICE's decision problem.
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	A cost-consequence analysis was conducted and justification for this is implied given that this type of analysis is required for submissions to MTEP.
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)?	Not clear	Details were provided on the use of the REMODEL data and use of data from the National Audit. Some assumptions were made regarding the extrapolation of data that were not fully supported by the evidence.
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?	N/A	
13. Were the details of the subjects from whom	N/A	

Study question	Response (Yes/No/Not clear/NA)	EAC comments
valuations were obtained given?		
14. Were productivity changes (if included) reported separately?	N/A	
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?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Not clear	Currency was reported. Cost years were provided for some costs, but not for others. It appears that the costs used within the model were not from a consistent price year.
19. Were details of price adjustments for inflation or currency conversion given?	No	No costs were reported to be inflated.
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	
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?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	

Study question	Response (Yes/No/Not clear/NA)	EAC comments
28. Was the choice of variables for sensitivity analysis justified?	Not clear	However, all inputs were varied ±20% rather than dependent upon their confidence interval.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared?	Yes	FESS is the relevant comparator, but Acclarent was also compared and this device is no longer available in the NHS.
31. Was an incremental analysis reported?	Yes	
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?	Not clear	The generalisability of input parameters to the current NHS was discussed and expert advice sought. The results were deemed to apply to the NHS. However, this was not explicitly discussed in relation to the model's results.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ (59). Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in healthcare. York: Centre for Reviews and Dissemination		