NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

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

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Newcastle and York to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 4pm, **15 April 2016** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 8 and 10: Statement that there is only weak indirect evidence to substantiate the equivalence of FinESS with XprESS	Reconsider the evidence that shows that FinESS and XprESS are equivalent devices.	The FinESS and XprESS are considered equivalent devices based on the fact that they include the same materials, overall design, and mechanism of action. The major difference is that the approach to access the sinus is transantral for FinESS and transnasal for XprESS. The approach has no impact on the devices' mechanism of action of dilation at the sinus ostium. As can be seen in Figure 4 of the Chandra et al (2016) paper, the change in SNOT-20 scores are similar whether the FinESS or XprESS device was used.	No change required. No head to head comparison of XprESS MSDS and FinESS were made. They have different indications, forms, and routes of administration. The EAC considers there was no evidence that they are equivalent or different.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 8: Statement that there is no published evidence on use of XprESS in subgroups is not accurate.	Although there is evidence supporting use of XprESS in a number of patient subgroups, there is limited evidence in the subgroup of patients with CRS with nasal polyposis.	The clinical studies provide evidence regarding the use of XprESS in a number of subgroups including patients with: CRS, RARS, multisinus disease, septal deviations, accessory ostia, and	The EAC's report has been updated to reflect this.

		anterior ethmoid disease.	

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p.8 and throughout document: Terminology correction.	Replace “balloon sinuplasty” with “balloon sinus dilation” or “balloon dilation”.	Entellus uses the terms “balloon sinus dilation” or “balloon dilation” to describe XprESS device procedures. The term “sinuplasty” is used by Acclarent Inc. as part of the name for their Relieva device.	This has been updated throughout, with the exception of reporting on search strategies.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 8, para 3: Clarification of FESS procedures.	The only experimental comparative evidence included by the company was the REMODEL randomized controlled trial (RCT), which compared balloon **sinus dilation** (XprESS MSDS or FinESS system) with functional endoscopic sinus surgery (FESS) **that consisted of maxillary antrostomy and uncinectomy, with or without anterior ethmoidectomy**.	Clarification that the FESS procedures included in the control arm of the REMODEL trial were limited to maxillary antrostomy and uncinectomy, with or without anterior ethmoidectomy.	No change has been made to the summary. However, this issue has been addressed in the main body of the report (Section 3.5.2).

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 8, para 3 and Section 3.5.2, p. 51: The REMODEL trial is referred to as a non-inferiority randomized controlled trial.	Delete the word “non-inferiority” from the sentence describing the REMODEL trial. Note that the change in SNOT-20 score was only one of 2 primary endpoints that were prespecified in the protocol.	The trial had 2 primary endpoints, one that was evaluated as a non-inferiority endpoint (SNOT-20 scores) and the other that was evaluated as a superiority endpoint (number of debridements per patient). As such, it is not accurate to refer to the entire trial as a non-inferiority randomized controlled trial.	No change required. The EAC considers that the SNOT-20 score was the primary outcome, as reported in clinicaltrials.gov. Non-inferiority was used for this outcome.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 9: The report states that the secondary endpoints were not prespecified in the protocol.	Revise the sentence to say that “**the prespecified secondary endpoints included: recovery outcomes, short-term improvement in sinus symptoms, complication rate, and revision rate**”.	The prespecified secondary outcomes were as reported by Cutler et al (2013) and were included in the protocol that was reviewed and approved by the IRBs and provided to the investigators. Because REMODEL was a postmarket study, posting on the clinicaltrials.gov website was not required and some of the study design information that the company wanted to keep confidential was not included in the	This has been reworded to clarify the secondary outcomes were not pre-specified on www.clinicaltrials.gov.

		posting.	

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 9: REMODEL data regarding the improvements in SNOT-20 scores and debridement are not the final data from the study as presented in Chandra et al.	The REMODEL trial reported statistically significant and clinically important Improvements in the SNOT-20 score in both the balloon dilation arm **(-1.60; n=74)** and the FESS arm **(-1.59, n=61) at 1-year follow-up.[4]** In patients **(n=135)** with uncomplicated CRS….. There was a statistically significant difference reported in the **second primary endpoint of the** requirement for subsequent nasal debridement in the balloon arm compared with FESS (**0.2 vs 1.0**, p<0.0001) **demonstrating superiority for balloon dilation**.	When summarizing the trial outcomes, the most current data should be reported (Chandra et al, 2016), whenever relevant. Also note that the debridement was a coprimary endpoint for testing for superiority.	No change required. This issue is present throughout the document. Although the Chandra paper reported on a bigger cohort of patients, the EAC considered that the reporting of outcomes was generally not as clear or complete in this paper as compared with the reporting on Cutler or Bikhazi. The EAC also considered the expansion of the cohort was poorly described in both the Chandra paper and the submission. For this reason, the EAC has tended to report results from the more more clearly reported Cutler paper. In most cases, there were no important differences between the papers. Where an important difference was observed, this was highlighted. Additionally, the EAC would emphasise that the summary only reports key data. In the opinion of the EAC, nasal debridement was not a primary outcome and had little relevance to the English NHS setting. The primary outcome of the REMODEL trial was change in SNOT-20 score at 6 months.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 9, 11, and 14: Missing information.	Additionally, there was evidence that balloon **sinus dilation** was associated with patient benefits such as improved recovery time, **less post discharge nasal bleeding**, and reduced requirement for **prescription** analgesia compared with FESS.	The reduction in nasal bleeding after discharge is an important finding that was not included.	No change. This data is reported fully in Section 3.6.2 of the assessment report.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 9: Use of the word “some” to describe the evidence of the REMODEL and Multi-Sinus studies lacks objectivity.	The XprESS Multi-sinus study provided evidence, **through a statistically powered** subgroup analysis, that the XprESS MSDS was effective in treating the maxillary, frontal, and sphenoid sinuses.	Both the REMODEL and XprESS Multi-Sinus studies were statistically powered to test the study hypotheses at 90% power and enrolled more than the minimum number of participants to meet the sample size requirement, therefore, the evidence is statistically strong for both of these studies. Although not included within the scope of the clinical evidence analysis, multiple studies using the Acclarent Relieva balloon support the findings of the XprESS Multi-Sinus study that balloon dilation is effective in treating the maxillary,	This has been reworded by the EAC.

		frontal and sphenoid sinuses.	

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 10: Concern over the REMODEL dropout rate.	**Although there was a higher rate of dropout after randomization (but before treatment) in the FESS arm than in the balloon arm, this did not impact the results of the primary endpoint of change from baseline in SNOT-20 score.**	The pre-specified statistical analysis plan for REMODEL did not intend to include data for participants without 12-month data available for the non-inferiority test for the change in SNOT-20 score. Therefore, no method of imputation was specified. To address the concerns of the EAC, a *post hoc* intent-to-treat analysis was performed based on all 151 randomized participants. Missing 12-month data was imputed from the last observation carried forward. Results of the analysis actually favour the balloon group (change from baseline, balloon -1.5 vs FESS -1.3), however, the overall conclusion remains the same: non-inferiority was still met (p<0.0001).	The EAC has made a small change to section 3.5.2 to reflect this new information. This post hoc imputation was not described in the published papers. The EAC maintains the high drop out rate immediately after randomisation is a limitation of the study.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 11:	Overall, the data showed that in a selected patient population, the use of balloon dilation is	The second primary endpoint of the	No change to the report. The EAC considered that the requirement for post-

Missing information.	associated with non-inferior QoL improvements compared with FESS, and this effect is immediate and continues for at least 2 years. **The data also show superiority of balloon dilation over FESS for the number of postprocedure debridements per patient.**	REMODEL trial was not included.	procedural debridement was not generalisable to the NHS (discussed in Section 3.5.3).

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 13: Weakness of REMODEL are overstated.	Clinical data derived from the REMODEL trial [4] was assumed to generalise to NICE's decision problem. There are **potentially** differences between the population in the REMODEL trial and the population described in the scope (see Section 3.5.3) **since the** study was set in the US.	The "mix of devices" (use of FinESS and XprESS) within the REMODEL trial is not a weakness as the devices are equivalent, as noted previously. The FinESS and XprESS include the same materials, overall design, and mechanism of action. The major difference is that the approach to access the sinus is transantral for FinESS and transnasal for XprESS. The approach has no impact on the devices' mechanism of action of dilation at the sinus ostium. As can be seen in Figure 4 of the Chandra et al (2016) paper, the change in SNOT-20 scores are similar whether the FinESS or XprESS device was used. Additionally, as noted previously, pre-specified statistical analysis plan for REMODEL did not intend to	EAC has reworded this section and section 3.5.2 of the report.

		include data for participants without 12-month data available for the non-inferiority test for the change in SNOT-20 score. Therefore, no method of imputation was specified. To address the concerns of the EAC, a *post hoc* intent-to-treat analysis was performed based on all 151 randomized participants. Missing 12-month data was imputed from the last observation carried forward. Results of the analysis actually favour the balloon group (change from baseline, balloon -1.5 vs FESS -1.3), however, the overall conclusion remains the same: non-inferiority was still met ($p<0.0001$). Therefore, these items should be deleted from the discussion of study weaknesses.	

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 14: Concerns over generalisability to NHS.	Reconsider the benefits within the NHS of moving the procedures for patients with uncomplicated CRS or RARS out of the OR and into the ambulatory setting. While this offers benefits to the patient, it also frees up limited OR resources for the patients that need them and reduces surgical wait times.	The EAC notes that the generalisability of the clinical evidence may be limited to a select population of patients seen in the NHS. The important point that is missed here is, that by treating the less complex cases in an ambulatory setting under local	No change to the report has been made. This claim was not clearly presented with the company's submission, hence there is no factual inaccuracy.

		anaesthesia will result in freeing up the limited OR time and resources for those patients who have more complex cases and require sinus surgery in the OR.	

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 14: Missing information.	Thus it supported the company's claim that balloon sinus dilation was non-inferior to FESS in terms of the primary outcome of QoL using the SNOT-20 **and superior to FESS for the primary outcome of reduction in postoperative debridements**.	The second primary endpoint of reduction in debridements was not included.	No change has been made. As discussed in response to issue 7 the EAC did not consider this outcome to be generalisable.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1, p. 15: Inclusion of recurrent acute rhinosinusitis is not relevant.	Overall, the EAC considers that whilst the evidence submitted by the company was largely internally valid, it will not generalise to all people within the NHS with chronic rhinosinusitis in whom all medical therapy has failed.	Delete the words "including recurrent acute rhinosinusitis". The clinical studies included patients with both CRS and RARS and subgroup analyses have demonstrated similar outcomes in both patient groups.	No change has been made as this is not a factual inaccuracy. The description has been left as it is for clarity and consistency with the scope.

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.1.1, p. 17: EAC noted that references were not provided.	The company would like to include the following references. 1. May M, Levine HL, Mester SJ, Schaitkin B. Complications of endoscopic sinus surgery: analysis of 2108 patients - incidence and prevention. *Laryngoscope*. 1994;104:1080-1083. 2. Rombout J, de Vries N. Complications in sinus surgery and new classification proposal. *Am J Rhinol*. 2001;15:363-370. 3. Levine HL, Sertich II AP, Hoisington DR, et al. Multicenter registry of balloon catheter sinusotomy outcomes for 1,036 patients. *Ann Otol Rhinol Laryngol*. 2008;117:263-270.	Although complications in the REMODEL trial were equal in both arms (0%), the general literature for FESS indicates a complication rate of approximately 1%. Rates for balloon dilation in the literature are <0.1%. References are now provided.	No change has been made. The EAC cannot accept additional literature following submission and critique as part of the fact check. However, if these studies are material to the decision problem then they could be appraised. This was not possible within the time frame of the factual check response.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.3.4, p. 28: The range of possible SNOT-22 scores is incorrectly stated as 0 to 100.	SNOT-22 scores are reported as the total score per patient, on a scale of 0 to **110**.	Each item is scored from 0 to 5, so with 22 items, the total possible score is 110, not 100.	Thank you, we have changed text accordingly.

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.3.4. Table 3.5 is referenced in a paragraph discussing secondary and healthcare related endpoint. The table referenced presents SNOT-20 outcomes.	Move the sentence to the preceding paragraph that discusses SNOT-20 scores	It is confusing to reference the table of SNOT-20 outcomes within the paragraph describing the secondary outcomes.	Thank you, we have corrected this error.

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.3.6, p. 30: EAC question of gross polyposis.	About two-thirds of patients receiving FESS in the NHS have nasal polyps, **although only one-third have gross (grade 3) polyposis.**	Gross polyposis is defined as grade 3 polyps resulting in total obstruction on 1 or both sides. Although the UK sinonasal audit stated that two-thirds of patients in the UK have nasal polyps, only about one-third of patients undergoing polypectomy have grade 3 polyps (Browne et al, 2003, table 5).	Thank you, the EAC has added this fact.

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.3.6, p. 30: Second bullet, the report has an incorrect reference number.	Correct the Brodner reference from number 34 to number 7.	The report incorrectly references the Brodner white paper [34] instead of the XprESS Registry paper, also by Brodner [7]	Thank you, we have corrected this.

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.3.6, p. 30: Report states that no results were reported for anterior ethmoid sinuses in the Multisinus study by Gould et al (2014). Additionally, the EAC's assessment that the study provided low quality evidence is inconsistent with the information provided by the EAC in table 3.4 (page 64) that the study has good methodological and reporting quality and has high applicability to the decision question.	The XprESS Multisinus study provides evidence of efficacy of balloon dilation for the treatment of maxillary, frontal, and sphenoid sinuses. Additionally, subgroup analyses from this study and the REMODEL trial included outcomes by the presence or absence of ethmoid sinus disease and demonstrated symptom improvements in patients with ethmoid sinus disease despite the lack of direct treatment by the balloon.	The design of the XprESS Multisinus study allowed subgroup analysis of patients treated with balloon dilation for different combinations of sinuses. Ethmoid sinuses are not directly treated with balloon dilation, so were not included in the primary groupings for comparison (combinations of frontal, sphenoid, and maxillary). However, table 5 in the paper reports the SNOT-20 outcomes for patients with and without ethmoid sinus disease and showed significant and clinically meaningful improvements at 1-year compared with baseline.	The EAC has amended the text. Table 3.4 does contain the following footnote: "Methodological quality relative to studies of this type. All single armed observational studies are subject to extensive sources of bias and confounding". We have clarified this in the text.

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.3.6, p. 30: The EAC incorrectly assumed that the outcomes reported in the white paper by Brodner (2013) were from the XprESS Registry study, and were therefore out of scope.	Patients with mild to moderate septal deviations were evaluated in a retrospective analysis of prospectively collected data reported by Brodner (2013). Outcomes evaluated were technical success, procedural comfort, and symptom improvements. Technical success was high (98%) and patients tolerated the procedure well under local anaesthesia. Symptom improvement was significantly improved in both groups. A subgroup analysis of the REMODEL trial also evaluated SNOT-20 outcomes in patient with or without mild to moderate septal deviations. No differences were observed in these subgroups (Cutler et al, 2013). Please correct table 2.1 accordingly.	The white paper by Brodner (2013) is a retrospective analysis of patients from multiple studies (BREATHE, FinESS Registry, RELIEF, XprESS Maxillary Pilot, and XprESS Multisinus). The data was prospectively collected but retrospectively analysed. The analysis supported the efficacy of balloon dilation in patients with mild to moderate septal deviations. Additionally the REMODEL trial reported favourable SNOT-20 outcomes for patients with and without septal deviations and with and without accessory ostia (Cutler et al, 2013).	The EAC has removed the erroneous citation to the Brodner White paper.

Issue 23

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.3.1, p. 41: The reference for the XprESS Multisinus Study is missing.	Insert reference number 6 for the Multisinus study by Gould et al (2013).	Reference is missing for the paper by Gould et al (2013) for the XprESS Multisinus study.	Thank you, this reference has been added.

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.3.2, p. 44: Exclusion of paper not out of scope.	Reconsider the exclusion of the Eloy et al (2012) paper as out of scope.	The EAC excluded the paper by Eloy et al (2012) [14] as being out of scope. The company contends that in the absence of any note of revision within the scope, it should not be automatically assumed to be out of scope. Use of balloons in revision surgery, especially frontal sinus surgery, is a safe and effective practice, as demonstrated within this small case series.	No change to the report has been made. There is an absence of comparative data to evaluate the efficacy and safety of revision surgery. Furthermore, there was no discussion of the efficacy of revision surgery at any point in the company's submission and it was not a claimed benefit.

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.3.2, Table 3.1: The 12-month sample size of 119 for REMODEL is incorrect.	The sample size at 12 months for the REMODEL trial should be listed as 130.	As reported in Table I of the paper by Chandra et al (2016), the sample size for the REMODEL trial at 12-months was 130 participants (71 balloon dilation and 59 FESS patients).	No change. In table 3.1 the EAC has reported both patient numbers from the Bikhazi paper and the Chandra paper. As stated earlier, due to the superior reporting in the Cutler and Bikhazi paper, and the fact the Cutler paper was the one that critically appraised (as it was the study that reported the methods), the EAC opted to use data from this study for

			shorter term outcomes.

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.3.2, Table 3.1: Only 1 of the 2 primary endpoints is noted for REMODEL.	Debridement frequency **(primary)**	The REMODEL trial had two prespecified coprimary endpoints. Both should be noted as such.	No change has been made. The EAC considers that nasal debridement was a prospective primary endpoint, for reasons discussed in the assessment report.

Issue 27

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.3.2, Table 3.1 (throughout): Productivity/reinfection is listed as an endpoint.	Change productivity/reinfection to **work productivity**	An endpoint measured in many of the studies was the work productivity as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire or the Work Limitations Questionnaire (WLQ). Reinfection is not part of the productivity endpoint.	The EAC has amended this.

Issue 28

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.3.2, Table 3.1 and Section 3.5.5, Table 3.4: The EAC judged the studies by Levine et al (2013) and Cutler et al (2011) to be of limited use and medium applicability to the decision problem based on the use of FinESS instead of XprESS.	Reconsider the EAC assessment of the usefulness of the RELIEF and BREATHE studies for the safety and efficacy of balloon dilation in CRS patients and the applicability to the decision problem based on the fact that both devices have similar materials, designs, and, most importantly, mechanisms of action; and outcomes from studies using the 2 devices showed no difference for the change in SNOT-20 score from baseline.	The EAC assessed the BREATHE and RELIEF studies as of limited use because the patients were treated with the FinESS device, not the XprESS device. These devices include the same materials, overall design, and mechanism of action. The major difference is that the approach to access the sinus is transantral for FinESS and transnasal for XprESS. The approach has no impact on the devices' mechanism of action of dilation at the sinus ostium. As can be seen in Figure 4 of the Chandra et al (2016) paper, the change in SNOT-20 scores are similar whether the FinESS or XprESS device was used.	No change. The EAC has noted there was no direct evidence of equivalence offered between these devices which have very different approaches as well as indications. The EAC has retained these studies as being in scope but has highlighted the uncertainty associated with doing so.

Issue 29

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.2, p. 53: The description of final attrition for REMODEL is incomplete.	…the EAC established from the company that only 3 **additional** patients in the FESS arm withdrew following randomisation, which was consistent with the initial cohort. A *post hoc*	There were a total of 16 participants who withdrew from the REMODEL trial after randomization but before undergoing the assigned procedure.	The EAC has made a text change to reflect the company's unpublished analysis. However, the initial attrition rate remains a limitation of the study.

	intent-to-treat analysis including all 151 patients confirmed the non-inferiority of the per protocol analysis (p<0.0001).	The pre-specified statistical analysis plan for REMODEL did not intend to include data for participants without 12-month data available for the non-inferiority test for the change in SNOT-20 score. Therefore, no method of imputation was specified. To address the concerns of the EAC, a *post hoc* intent-to-treat analysis was performed based on all 151 randomized participants. Missing 12-month data was imputed from the last observation carried forward. Results of the analysis actually favour the balloon group (change from baseline, balloon -1.5 vs FESS -1.3), however, the overall conclusion remains the same: non-inferiority was still met (p<0.0001).	

Issue 30

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.2, p. 53: The 27% follow-up for REMODEL at 24 months is incorrect.	Replace “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]” with the following: **Additionally, 66 and 25 participants (100% of those eligible) were followed to 18 and 24 months, respectively.**	As designed, all participants in the REMODEL trial were to be followed for 12-months post procedure for the primary endpoint. To gather additional longer-term data, each participant who completed the 12-month visit was to be followed every 6 months until the study closed (when all participants had completed the 12 month visit).	No change has been made. The EAC has made no factual errors. It is appropriate to highlight that the 24 month data was underpowered, and no protocol or rationale was provided for the closure date of the study.

		Therefore, at the time of the study closure, there were 66 participants who had completed 18-month visits and 25 who had completed 24-month visits. Both of these follow-up periods included 100% of the participants who were eligible for the follow-up. The long-term results of these participants are consistent with the rest of the study data.	

Issue 31

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.2, p. 53 and p. 60, Table 3.3: Outcomes and statistics. Power calculation for debridement was described as *post hoc*.	Remove the statement regarding the power calculation for the debridement outcome. In Table 3.3, remove statement that the frequency of nasal debridement "was not pre-specified in research protocol."	The sample size calculation for the debridement endpoint was prespecified in the protocol. Although the secondary endpoints (as reported by Cutler et al) were not listed on clinicaltrials.gov website, they were included in the protocol that was reviewed and approved by IRBs and provided to the investigators. The power was 90%, alpha=0.025, estimate for balloon dilation=0.5, estimate for FESS=1.0, and SD=1.0 for both groups.	The EAC has removed reference to post hoc analysis as this was speculative. The EAC has not received the protocol submitted to the IRB. The material presented by the EAC is factually correct based on the published manuscripts.

Issue 32

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.3, p 56: The report incorrectly states REMODEL is limited to a single maxillary sinus.	Replace "Given that the REMODEL study is limited to a single maxillary sinus with some anterior ethmoid surgery in some patients the Lund-Mackay scores would be expected to be low." with the following: "Given that the REMODEL study is limited to treatment of patients with unilateral or bilateral maxillary sinus disease with or without anterior ethmoid disease, the Lund-Mackay scores would be expected to be low."	The REMODEL trial allowed participants with bilateral or unilateral maxillary sinus disease with or without anterior ethmoid disease (only the maxillary sinuses were treated). Virtually all of the participants had bilateral maxillary disease as can be determined from a total of 146 sinuses treated in a total of 74 balloon arm participants. The REMODEL trial was intentionally limited to maxillary sinus disease with or without anterior ethmoid disease due to statistical and sample size considerations. However, the XprESS Multisinus study demonstrated that patients with other sinus disease also responded favourably and durably to balloon dilation. The approved labelling for XprESS is for treatment of the frontal, maxillary, and sphenoid sinuses. Therefore, patients treated with XprESS are not limited to those with isolated maxillary disease and low MacKay scores.	This has been corrected.

Issue 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.4, Table 3.3: The report states that SNOT-20 scores could be influenced by clinicians.	SNOT-20 is a subjective primary outcome and could be influenced by the **participant's perceptions**.	The SNOT-20 questionnaire is a patient-reported outcome. The patient completes the questionnaire independently of the clinician. So although the questionnaire is a subjective measure, it is not influenced by the clinicians. Additionally, the consistency of the outcomes over long-term follow-up decrease the likelihood that the outcomes were biased.	The EAC has amended Table 3.3 accordingly.

Issue 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.5, page 62: XprESS Registry. Missing information.	Patients (n=175) were enrolled if they required treatment of the frontal recess, sphenoid ostium, **and/or maxillary ostium/ethmoid infundibulum**. **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.**	Early in the study, the indication for use of the XprESS was limited to frontal and sphenoid sinuses. However, soon after the start of the study the indications were modified to include the maxillary sinuses, so participants in the study could have balloon dilation of the frontal recess, sphenoid ostium, and maxillary ostium and anterior ethmoid infundibulum. Outcomes are not listed for the	EAC has updated the report to include the revised text.

		correct time periods.	

Issue 35

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.5, p. 63: RELIEF study. Missing information.	The primary outcome of this study was QoL as measured by the SNOT-20 **and RSI. Other outcomes measured included technical success, revision rate, and safety**. **A strength of this study was the subgroup comparison of patients with CRS vs RARS.**	Incomplete information is provided regarding the study outcomes. Also reconsider the statement of limitation due to use of FinESS as noted above.	The EAC has updated its report for this.

Issue 36

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5.5, p. 63: The report incorrectly includes the WPAI and WLQ as primary endpoint of the BREATHE study.	**Primary outcomes were improvement in sinus symptoms (as measured by the SNOT-20), ostial patency at 3 months, and device-related safety.** Follow-up was up to 2 years **post procedure. A secondary paper reported outcomes of work productivity questionnaires (WPAI and WLQ) at 1-year follow-up.**	The primary endpoints of the BREATHE study were change in SNOT-20 scores, ostial patency (by CT scan), and device-related safety. Work productivity was a secondary endpoint that was published as a secondary manuscript.	The EAC has updated its report for this.

Issue 37

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.2, Table 3.5: Some inaccurate values. No references.	Baseline pre-procedure XprESS = 2.54 ± 9.**2** 1 week XprESS = -1.4**9** ± 0.87 1 week FESS = -0.9**6** ± 1.12 Footnote *** Statistically significant difference between XprESS and FESS arms (p=0.**0**14)	Some values are not as reported in the relevant paper. Additionally, because the values in the table are taken from multiple papers, each time point in the table should reference which paper was used to provide the value.	The table has been updated for the errors in number highlighted where these could be verified within the published paper.

Issue 38

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.2, page 68: The report notes the discrepancies between the published report by Bikhazi et al (2014) and the submission.	We suggest use of the data from the paper by Chandra et al (2016) whenever possible or relevant since this is the most current and complete dataset.	The discrepancies noted can be explained by the fact that the submission included the most current data from the REMODEL trial on 135 participants that was published by Chandra et al (2016). The EAC report tends to include the data from the earlier study of 92 participants as reported by Cutler et al (2013) or Bikhazi et al (2014).	No change has been made. The EAC has provided the reasons for these discrepancies in the report. The EAC has been consistent in its approach to using published data where possible.

Issue 39

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.2, page 68: The report includes incorrect data regarding the outcome of nasal bleeding.	In the study, the authors also report a significant reduction in nasal bleeding after discharge in the balloon group compared with the FESS group (32% vs 56%, p=0.009).[4]	The counts and percentages in the report are those reported in Table 3 in the paper by Cutler et al (2013); however, the p value is that reported by Chandra et al for percentages of 32% vs 56%. As noted before, the data from the Chandra paper is the most current and complete data from the REMODEL trial and should be used whenever possible.	No change has been made. For reasons discussed under issue 7, the EAC considers it most appropriate to report on data from the fully published and critically appraised paper by Cutler et al, rather than possibly selected data in Chandra et al.

Issue 40

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.2, p. 68: The report fails to note the technical success endpoint.	Technical success was achieved in 99.3% (145/146 attempted sinuses) for balloon dilation.	Technical success is an important endpoint in all the balloon dilation trials and should be reported as an outcome for REMODEL.	The report has been updated to include technical success.

Issue 41

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.2, p. 69:	Note that there was no statistically significant	Again, the discrepancy noted is due	The report has been amended for this.

Discrepancy noted in ostial patency data.	difference between treatment groups for ostial patency at 1 year in the results published by Chandra et al (2016).[4]	to the difference in cohorts between the Bikhazi and Chandra papers. It should be noted that the data reported in Chandra et al was also not statistically significant between treatments.	

Issue 42

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.3, new section: Missing information.	These results are supplementary or supporting to the comparative efficacy data, and are particularly useful in the measurement of technical success, safety outcomes, **and the 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, debridements, healthcare utilization, and work productivity**, have been synthesised in a **published** meta-analysis, and are discussed in Section 3.8.	We would argue that the change in QoL (SNOT-20), which was reported in all the studies, is an important measure providing supplementary or supportive information to the REMODEL. Additionally, the published results of the meta-analysis included more than just the SNOT-20 and WLQ outcomes.	The report has been amended for this.

Issue 43

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.3, new section: Missing information.	In the study, **22 patients underwent maxillary, frontal, and sphenoid balloon dilation**; 32 underwent maxillary and frontal dilation; 5	Description of the breakdown of participants by sinus for the Multisinus study is missing those	The report has been amended for this.

	underwent maxillary and sphenoid dilation; and 22 underwent maxillary dilation only. **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**. **This 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.**	treated for maxillary, frontal, and sphenoid sinus disease. Additionally, the mean change in SNOT-20 scores is a significant outcome that was not reported. Furthermore, several important subgroup analyses were performed, including CRS vs RARS, by baseline LM scores, and by the presence or absence ethmoid disease, septal deviations, and turbinate reductions.	

Issue 44

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.3, new section: The report describes the Multisinus Study evidence as exploratory.	The subgroup comparisons reported in the XprESS Multi-Sinus Study provide 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 generalizable to a broader population **of patients with uncomplicated multi-sinus disease**.	According to the sample size calculation for the multisinus study, a minimum of 19 patients was required to adequately test the study hypothesis with 90% power. Given that all but 1 of the treated sinus combinations (maxillary and sphenoid) included more than 19 patients, the description of this study as exploratory does not seem accurate.	The EAC has removed the term exploratory.

Issue 45

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.3, new section: Incorrect date of publication, incorrect numbers of patients treated with hybrid procedures, and redundant description of a hybrid procedure. Missing outcome.	The XprESS Registry by Brodner et al (**2013**)[7] used hybrid **procedures** as the intervention in a large majority of patients (**156/175**), with 10 patients not receiving balloon **sinus dilation**, and 9 patient receiving only standalone balloon treatment. However, results were similar to the other observational studies empl**o**ying standalone balloon **sinus dilation**, including statistically significant reductions at **12** months in SNOT-20 score (-1.1), medication use, work or school days missed, **and** sinus-related physician visits. **Technical success was 96% (479/497 sinuses)**.	Correction of a typographical error for the date of publication from 2103 to 2013. Correction of the number of patients treated with hybrid procedures from 157/166 to 156/175. The definition of a hybrid procedure is use of a balloon dilation device within a FESS procedure, so saying “hybrid balloon and FESS surgery” is redundant. Technical success outcome was missing.	The report has been corrected for this.

Issue 46

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.3, new section: Clarification regarding RELIEF study.	The RELIEF study by Levine et al (2013)[9] investigated the use of **standalone balloon dilation using** 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	A unique feature of the RELIEF study was the reporting of the CRS and RARS patients separately, so statistical comparisons could be made between these patient groups. The subgroup analysis by disease location is also important.	The report has been amended for this.

	meaningful reduction in SNOT-20 score**s** (**-1.1 for CRS and** -1.2 **for RARS patients**) compared with baseline. Additionally, statistically significant reductions in RSI major symptoms; medication use (**ICS, antibiotics**); absenteeism; sinus-related physician visits; and acute sinus infections were reported. **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.**	Lastly, the antihistamine use was not statistically reduced as measured by the RSI (although the ICS and antibiotics were significantly reduced).	

Issue 47

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome number of post-procedure rhinosinusitis episode requiring medication, incorrect value.	No statistically significant difference between arms (reduction of 4.2 and **3.7** episodes per year for balloons and FESS, **p=0.258**).**[4]**	Correction of value from 3.5 to 3.7 and inclusion of p value. Reference added for REMODEL Chandra paper.	No change to the report has been made. The EAC have reported data from Cutler *et al*. as per the response to issue 7.

Issue 48

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome number of post-operative debridements, incorrect	Mean number of post-procedure debridements per patient was statistically significantly lower in the balloon arm compared to FESS (**0.2 vs 1.0, p<0.0001**). Similar low rate in **meta-analysis**	The debridement on the final cohort of REMODEL patients is provided by Chandra et al (2016)[4]. The value of 0.16 is from the meta-	The report has been updated, where appropriate.

p value and incorrect reference.	**(0.16 ± 0.55).** **Add reference [4]**	analysis, not the BREATHE study (which reported a debridement value of 0.03).	

Issue 49

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome change in ostial patency, missing relevant study.	**Ostial patency of 90.6% reported at 3-months in the BREATHE study.** **Add reference to Cutler et al (2011) [10]**	Ostial patency was also measured in the BREATHE study.	This has been updated.

Issue 50

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome duration of analgesic medication. Most current information not provided.	Significant reduction in the number of days on prescription pain medications with balloon dilation compared with FESS (**1.0 vs 2.8 days, p<0.0001). Over the counter analgesic use was not statistically different between balloon and FESS.** **Change reference to Chandra et al (2016)[4]**	The analgesic use on the final cohort of REMODEL patients is provided by Chandra et al (2016)[4].	No change has been made as per previous responses regarding the publication used for REMODEL trial data.

Issue 51

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome patient-reported tolerance of the procedure and/or patient reported severity of pain scale. Missing relevant information.	**Pain scores measured on a VAS from 0 (no pain) to 10 (severe pain) ranged from 1.8 to 3.2 across 4 studies. The meta-analysis provided a mean procedure pain score of 2.6 indicating good tolerability.** **Add reference for Chandra et al (2016)[4]**	Although there is no comparative day to FESS, the pain scores are still of value to demonstrate that the patients tolerate the balloon procedure well. The only Acclarent study reporting pain scores for balloon dilation indicated a mean value of 4.5.	The meta-analysis VAS data has been added into the report.

Issue 52

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome length of hospital stay. Missing information on recovery times.	**In the REMODEL trial, recovery times (return to normal activities) averaged 1.5 days for balloon dilation and 5.0 days for FESS.** **In the BREATHE trial, 88% of patients were back to normal activities within 2 days of the procedure.** **The meta-analysis confirmed the balloon dilation value with a mean recovery time of 1.4 ± 1.3 days.** **Add reference to Chandra et al (2016)[4]**	Length of hospital stay is not applicable to the studies performed primarily in physician offices. Time to recovery of normal activities was measured in a couple of the studies and is a more relevant measure for this procedure, which can be performed under local anaesthesia. According to the UK sinonasal audit, the median time to return to work was 2 weeks and nearly 55% of patients were not back at work until after 2 weeks and up to 4 weeks.	No change has been made as the EAC reporting is factually correct. This data was not provided or discussed by company in the clinical evidence section of the submission

Issue 53

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome success rates of maxillary sinus ostial cannulation, missing appropriate reference.	**Add reference to Chandra et al (2016)[4]**	The values listed are from the publication by Chandra et al (2016) but the reference is not provided.	Thank you; we have changed the citation to reflect this.

Issue 54

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome rate of revision surgery, missing values and clarification needed.	Rate of revision low in all studies, no statistically significant difference between balloon and FESS arms **at 1 year (1.4% vs 1.7%). One-year** revision rate **for single-arm pooled balloon studies was** 3.2% in meta-analysis**.**	Provided values for 1-year revision rates for REMODEL balloon and FESS arms. Clarified that the 3.2% value is specific to the 5 single-arm observational balloon dilation studies (excluding REMODEL balloon arm).	This amendment has been made.

Issue 55

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome rate and severity of nasal bleeding, most current data not provided.	Nasal bleeding after discharge reported in 4 studies and the meta-analysis. **In REMODEL, the** rate of bleeding after discharge significantly higher in patients who	Rates of nasal bleeding after discharge on the final cohort of REMODEL patients and in the meta-analysis are provided by	The EAC has added the summary data from the meta-analysis in the table.

	had received FESS than compared with those receiving balloons (**32% vs 56%, p=.009). In the meta-analysis, 13.8% (32/232) of balloon dilation patients reported nasal bleeding after discharge.** **Add reference to Chandra et al (2016)[4]**	Chandra et al (2016)[4].	

Issue 56

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.6: Outcome device-related adverse events, missing information	**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.**	Information on the only serious adverse event reported in any of the clinical studies has not been included (subcutaneous emphysema in the BREATHE study).	The EAC has added this text.

Issue 57

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, p. 75: Incomplete information	XprESS MSDS was also statistically equivalent to FESS in maintaining ostial patency, demonstrating a similar low requirement for surgical revision**, improving work productivity, reducing rhinosinusitis episodes, and resulting in very rare safety events.** There is evidence that compared with FESS, XprESS MSDS **significantly** reduced recovery times, the need for prescription	The listing of overall outcomes was incomplete.	The EAC has amended this text.

	analgesia, **the number of postoperative debridements, and the occurrence of nasal bleeding after discharge**.		

Issue 58

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.4, Table 3.7: Claimed patient benefits, faster recovery time with less nasal bleeding and shorter duration of need for pain medication, incorrect comparison.	REMODEL demonstrated reduced nasal bleeding and reduced prescribed (but not OTC) analgesia compared with **FESS.**	The REMODEL trial comparison as stated should be against FESS, not XprESS MSDS.	This correction has been made.

Issue 59

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6.3, p. 77: Conclusion questioned.	However, as discussed, the EAC would caution that there may be issues with generalizability to the UK NHS with the current comparative evidence base for XprESS.	The report states that “the current comparative evidence base for XprESS is limited in terms of power and there may be issues with generalizability.” However, 135 patients were treated in the REMODEL trial, a number far exceeding the minimum number of patients (36/arm) required to test the study hypothesis at 90% power. This was a statistically powered study.	This comment referred to the later time point (24 months). The text in Section 3.6.5 has been amended.

Issue 60

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.7, p. 80: Clarification.	This **is** the same event reported by the company in Section 7.7.2 of their evidence submission [10].	The report states that the event of swelling of the face and neck "**may be** the same event reported by the company in Section 7.7.2 of their evidence submission." The company can confirm that this is true.	The text within the report has been updated.

Issue 61

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.8.1, p. 84: Clarification.	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 **sinus dilation** arm of the REMODEL trial, and 3.2% for the pooled analysis **of the single-arm balloon dilation studies**.	Clarification that the 3.2% is referring to the pooling of the single-arm studies only, not including the REMODEL balloon dilation arm. The paper also notes that there was no statistical difference when the REMODEL was included in the pooling, but the percentage was not published.	The text within the report has been updated.

Issue 62

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.10, p. 86: The report is missing the outcome of nasal bleeding.	Furthermore, there was evidence that balloon **sinus dilation** offered advantages over conventional FESS by speeding recovery, reducing postoperative pain, reducing the requirement for nasal debridement., **and reducing the occurrence of postdischarge nasal bleeding.**	The reduction in nasal bleeding after discharge is an important finding that was not included.	This text has been added to the report.

Issue 63

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.102, para 3: "The company reported that the model took an NHS perspective, but did not report the cost year of the analysis."	Follow by "The company subsequently clarified that the majority of the costs were for the year 2014/15. Where there was uncertainty over the costs these costs were not inflated"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 64

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.102, para 5: "The company noted training costs were excluded from the	Follow by "The company subsequently clarified that this cost was omitted as this was expected to be	Add for clarification	No update has been made. This is not a factual inaccuracy. The company's revised model, submitted during the factual check, will not be considered by

model as training is provided by Entellus.”	negligible. On reflection this assumption was revised to incorporate the EACs recommended approach in a revised submission”		the EAC except where factual inaccuracies are highlighted.

Issue 65

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.105/6: “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.”	Follow by “The company subsequently clarified that this had not been explored in a sensitivity analysis as it was reported explicitly in the breakdown of the model results; therefore, the impact was shown to be minimal.”	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 66

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 106, para 1: "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]."	Follow by "This number had been incorrectly reported in an internal document which was transferred to the model. On checking this, this assumption was revised to incorporate the EACs recommended value in a revised submission"	Add for clarification	No update has been made. This is not a factual inaccuracy. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

Issue 67

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 106: "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	Follow by "The company subsequently clarified that this had not been explored in a sensitivity analysis as it was reported explicitly in the breakdown of the model results; therefore, the impact of this could be seen to be minimal."	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification or justification made by the company during the factual check is not permitted.

model."			

Issue 68

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 215, Table 4.3: Reference to revision rates at 12 months "This value has been incorrectly extracted by the company and should be 4.7%."	Follow by "The company subsequently clarified that this had been incorrectly extracted. As this incorrect value was within the range explored in the sensitivity analysis and did not change the results the impact of this was expected to be minimal."	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 69

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.111, last paragraph: "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. Deriving revision rates from very rare events is subject to great uncertainty, hence the confidence interval around these revision rates (estimated by the	Follow by "The company subsequently clarified that this uncertainty had been captured in the sensitivity analysis as the higher limit with XprESS overlapped the base-case with FESS. Nonetheless the company accepted that this criticism was valid and applied the EAC's recommended approach in a revised submission"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

EAC, rather than reported in the paper) are wide."			

Issue 70

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.111, last paragraph: "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. 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."	Follow by "The company subsequently clarified that this uncertainty had been captured in the sensitivity analysis as the higher limit with XprESS overlapped the base-case with FESS. Nonetheless the company accepted that this criticism was valid and applied the EAC's recommended approach in a revised submission"	Add for clarification	This is a repetition of issue 69, so please see the EAC response under that comments.

Issue 71

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.112, para 3: As such, the EAC judges that the evidence and advice does not support any significant difference	Follow by "The company subsequently clarified that assumption had been vetted with clinical experts in the UK and was supported.	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's

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].	Nonetheless the company accepted that there was uncertainty around this assumption and applied the EAC's recommended approach in a revised submission"		revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

Issue 72

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.114: "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. "	Follow by "The company subsequently clarified that this had not been explored in a sensitivity analysis as it was reported explicitly in the breakdown on the model results therefore the impact of this could be seen to be minimal."	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 73

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.117: "This cost includes the unit cost of a prescription in additional to drug costs, hence these costs are double counted."	Follow by "The company subsequently clarified that as the PSSRU report this cost separately to the unit cost of a GP appointment this has been assumed to be an additional cost. The company accepted that this criticism was valid based on the explanation provided and applied	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

	the EAC's and applied the recommended approach in a revised submission"		

Issue 74

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.118. Table 4.5: "Costs from NHS reference costs 2014/15 would have been most appropriate."	Follow by "The company subsequently clarified that they believed the 2011 price to be more valid than the costs in 2014/15 as costs in this year reflect the average costs and reference prices in subsequent years reflect payment by results tariffs. The cost had not been inflated due to uncertainty around this costs however the company accepted that this may have been appropriate here. In a revised submission the company applied the unit cost recommended by the EAC"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

Issue 75

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.118/119: "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	Follow by "The company did not agree with this approach as XprESS is expected to displace the majority of the FESS procedures reported in the articles and therefore this assumption should not be adjusted. Asking the expert to revise their estimate in a second interview also potentially	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The duration of FESS surgery used by the EAC was based upon expert advice in patients who would otherwise be eligible for

therapy."	introduces bias into this approach for seeking input"		balloon therapy. The EAC acknowledges the limitations with using expert opinion to inform model inputs. These are discussed in Section 4.6 of the report.

Issue 76

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 118/119: 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.	Follow by "The company did not agree with this approach and suggested that this assumption be revised to 73 minutes. The company submitted additional detail to clarify why this assumption is not aligned with other published estimates for the procedure time with FESS."	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The EAC have provided further clarification below: Expert advice received by the EAC stated that balloon therapy is not appropriate for all patients who would otherwise undergo FESS. This is consistent with the clinical evidence around XprESS MSDS whereby in the majority of studies patients with severe polyposis were excluded. Therefore, the EAC utilised the experts' judgement on procedure time in comparable patients. The procedure time was consistent with 3 sources of published evidence set in the NHS. However, we do note definitions of surgical time are not always clear The company provided the EAC with

			three clinical evidence sources to support their suggestion. The EAC judges that these sources are less applicable then the evidence used in the base case (for the reasons specified below). The FESS procedure times quoted within these papers are within the range considered within the EAC's threshold analysis. The data in the Cornet *et al*. (2012) are less relevant than the data used by the EAC as the patient population had chronic rhinosinusitus with nasal polyposis. The clinical experts contacted by the EAC reported that patients with nasal polyps would be less likely to be recommended for balloon dilation and the population of interest in this report is those eligible for balloon therapy. Further, the source is not from the NHS. Gibbons *et al*. (2001) report procedure times for FESS in patients with refractory chronic rhinosinusitus but the procedure also included complementary procedures (septoplasty, turbinate procedure) and/or supplementary procedure and turbinate reduction was also performed. This study then reports surgery times for FESS that include additional procedures. Further, the study was not set within the NHS. The Marzetti *et al*. (2014) patient population was patients with sinus

			headache (attributable to rhinosinusitis). This is not fully aligned with the patient population in the scope. Inferior turbinate reduction was performed as part of the FESS surgery of the frontal sinus in all cases. Further, the study was not set within the NHS.

Issue 77

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.118/119: "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 [15]"	Remove	This sentence should be removed as this misrepresents the reference. Further details of references supporting higher procedure times with FESS are provided as an appended submission.	The company has not provided information on why the reference has been misinterpreted. The EAC has re-checked the reference and confirms that 39.6 minutes refers to mean surgical time (knife to skin to descrubbing) for all operations. For sinus only operations (with no polyp removal) the procedure time is reported to be 41.5 minutes. The assessment report has been updated to clarify this point. However, the EAC notes that 41.5 minutes is still lower than the average duration of FESS estimated from the clinical expert's values of 42.5 minutes and therefore the value used in the EAC's base case.

Issue 78

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.119: "Cost of a surgeon of £1.77 per minute. This cost has been correctly extracted from Personal Social Services Research Unit (PSSRU) [78]. 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."	Follow by "The company subsequently clarified that as the unit cost in the source applied for theatre time did not specify this cost, this was assumed to be additional. Given this uncertainty, the company applied the EAC's recommended source for surgical time and excluded this cost in a revised analysis"	For clarity	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

Issue 79

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 119: "Cost of a nurse of £1.47 per minute. This cost has been correctly extracted from PSSRU [78]. 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	Follow by "The company subsequently clarified that as the unit cost in the source applied for theatre time did not specify this cost, this was assumed to be additional. Given this uncertainty the company applied the EAC's recommended source for surgical time and excluded this cost in a revised analysis"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

included within the operating theatre costs used by the company."			

Issue 80

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.119: "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."	Follow by "The company subsequently clarified that as the unit cost in the source applied for theatre time did not specify this cost, this was assumed to be additional. Given this uncertainty the company applied the EAC's recommended source for surgical time and excluded this cost in a revised analysis"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

Issue 81

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.119/118: Tray and camera costing £35 per surgery. The company correctly extracted the tray cost from the NHS Institute for Innovation and Improvement [81]. General consumable costs are already	Follow by "The company subsequently clarified that as the unit cost in the source applied for theatre time did not specify this cost, this was assumed to be additional. Given this uncertainty the company applied the EAC's recommended source for surgical time and excluded this cost	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual

included within the ISD Scotland theatre cost, but it is unknown whether they are included within the operating theatre costs used by the company.	in a revised analysis"		inaccuracies are highlighted.

Issue 82

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.119/118: Tray and camera costing £35 per surgery. The company correctly extracted the tray cost from the NHS Institute for Innovation and Improvement [81]. 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.	Follow by "The company subsequently clarified that as the unit cost in the source applied for theatre time did not specify this cost, this was assumed to be additional. Given this uncertainty the company applied the EAC's recommended source for surgical time and excluded this cost in a revised analysis"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The company's revised model, submitted during the factual check, will not be considered by the EAC except where factual inaccuracies are highlighted.

Issue 83

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 122. Table 4.6: "Clinical experts. Average of 2 experts providing advice on *both* FESS and XprESS MSDS (40	Follow by "The company did not agree with this approach and supplied additional information explaining	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The EAC have

and 45 mins) and a third experts stating FESS does not take much longer than 30 minutes."	why this assumption was not appropriate"		provided further clarification on issue 76.

Issue 84

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 126. Table 4.9: Value of 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]"	Follow by "The company did not agree with this approach and supplied additional information explaining why this assumption was not appropriate"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The EAC have provided further clarification on issue 76.

Issue 85

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 126. Table 4.9: Unit cost of ambulatory theatre time	Follow by "The company did not agree with this approach and supplied additional information explaining why this assumption was not appropriate"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The EAC have already acknowledged within the report that the operating theatre cost for procedures under local anaesthetic may be overstated, hence scenario analyses were conducted.

Issue 86

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p 127. Table 4.10: Value for procedure time with XprESS	Follow by "The company did not agree with this approach and supplied additional information explaining why this assumption was not appropriate"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted. The EAC have already acknowledged within the report that the operating theatre cost for procedures under local anaesthetic may be overstated, hence scenario analyses were conducted.

Issue 87

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 129: "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."	Follow by "The company subsequently clarified that this approach was appropriate for the majority of the model inputs where there was uncertainty but this was not expected to change the model results. For all inputs expected to be main drivers of the model this was tested by applying alternative assumptions (for example, two values for the unit cost of surgical time were considered) or exploring in breakeven analysis (for example for the procedure time with XprESS and FESS)"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 88

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 130: "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."	Follow by "The company subsequently clarified that the impact of a non-significant difference was captured in the DSA as the upper limit with FESS overlapped the base-case input with XprESS and the lower limit with XprESS overlapped the base-case with FESS. Given the uncertainty around the data, this approach was expected to be suitable for this type of analysis."	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 89

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.130: "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."	Follow by "The company subsequently clarified that this had not been explored in a sensitivity analysis as it was reported explicitly in the breakdown on the model results therefore the impact of this could be seen to be minimal."	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 90

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 139: "First, the company has assumed revision surgery occurs more frequently in patients treated with FESS than with XprESS MSDS."	Follow by "The company subsequently clarified that this assumption was expected to be justified as it was based on the direction of effect reported in REMODEL and supported by the experts they consulted. Furthermore, it should be acknowledged that the uncertainty around this assumption was explored by 1) running the model at different time horizons where a time horizon of 1 year excludes are costs beyond 1 year ad 2) varying the model inputs by 20% where any differences between FESS and XprESS was shown by overlapping confidence intervals"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 91

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 139: "Second, within its analysis the company assumed that the clinical data derived from the REMODEL study generalise to the decision problem outlined by NICE."	Follow by "This assumption was justified by the company in their response to the EAC interpretation of the clinical evidence"	Add for clarification	No change has been made. The EAC judges that issues regarding the generalisability of the US data to the NHS exist.

Issue 92

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 139: "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"	Follow by "The company noted this as a limitation in their analysis. The company also clarified that they did search for additional sources for unit costs for CRS surgery under local anaesthesia however none were identified. In the absence they submitted a revised analysis applying a very conservative assumption for the reduced cost of surgical time if procedures were conducted under local in the ambulatory setting the staff and facility overheads are expected to be considerably lower.	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 93

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 139: "First, an inconsistent cost year has been used throughout the model, in that all costs have not been inflated to the current cost year."	Follow by "The company provided a rationale for their assumptions. They also accepted the EACs recommendation and revised all unit costs to reflect the EAC's recommendation, with the exception of the unit cost of surgical time under local where they suggested an alternative assumption"	Add for clarification	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 94

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 139: "First, an inconsistent cost year has been used throughout the model, in that all costs have not been inflated to the current cost year."	Follow by "The company clarified that cost were not inflated where these was uncertainty around the estimate. They also accepted the EACs recommendation and revised all unit costs to reflect the EAC's recommendation, with the exception of the unit cost of surgical time under local where they suggested an alternative more conservative assumption"	Add for clarification	This is a repeat of issue 93. Please see the EAC response under that issue.

Issue 95

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"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"	This should be rephrased as follows "The company did attempt to conduct a cost-analysis comparing XprESS to Acclarent, noting a number of limitations around this analysis due to the lack of comparative data as well as lack of relevance to NHS decision makers as this device. For these reasons this analysis was not reviewed by the EAC"	This should be rephrased as is not fully accurate	No update has been made. This is not a factual inaccuracy so further clarification made by the company during the factual check is not permitted.

Issue 96

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 167: Clarification of information.	This study was published in 3 peer-reviewed papers at follow-up time of 6 months [2], 12 months [3], **and a larger cohort with up to** 24 months of follow-up [4].	The paper by Chandra included a larger cohort of patients than was reported in the earlier 2 REMODEL papers.	No change has been made as this is not a factual inaccuracy. This is explained in detail earlier in the report.

Issue 97

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 167: Duplicate references.	Additionally, a series of single-arm observational studies reported on XprESS MSDS or the FinESS system [**6**,7,**8**,9,10,12]	Reference number 49 is a duplicate of reference 8 and reference 92 is a duplicate of reference 6.	Thank you for highlighting this, the reference has been updated.

Issue 98

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 167: Incorrect assumption that the high attrition rate in the FESS arm between randomisation and treatment subsequently required a per protocol analysis.	The internal validity of the study was generally acceptable.	The pre-specified statistical analysis plan for REMODEL did not intend to include data for participants without 12-month data available for the non-inferiority test for the change in SNOT-20 score and no method of imputation was specified. To address the concerns of the EAC, a *post hoc* intent-to-treat analysis was	The EAC has changed the term per protocol to post hoc modified ITT analysis to more clearly reflect what appears to have happened in the study. The EAC has added a brief description of this post hoc analysis to results section; we do not believe further discussion belongs in the conclusion.

		performed based on all 151 randomized participants. Missing 12-month data was imputed from the last observation carried forward. Results of the analysis reject the null hypothesis and demonstrate that non-inferiority was met ($p<0.0001$). Therefore, the attrition had no impact on the study outcome.	

Issue 99

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Reference to generalisability of FinESS to XprESS results.	Delete the reference to the FinESS system.	As noted previously, the FinESS and XprESS are equivalent devices with regard to patient outcome.	No change to the report has been made. The EAC does not accept that equivalence of the technologies have been proven and this remains an area of uncertainty that should be highlighted. Hence, this is not a factual inaccuracy.

Issue 100

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Missing and duplicate references.	Evidence on change in rhinosinusitis symptoms and their impact was available from 6 studies reported on in 9 publications [2,**3**,4,**6**, 7,**8**,9,10,12].	Reference 3 (Bikhazi et al, 2014) was missing from the listing in the text. As noted previously, reference number 49 is a duplicate of reference 8 and reference 92 is a	Thank you for highlighting this, the reference has been updated.

		duplicate of reference 6 (we assume reference 93 was listed in error and was meant to be reference 92).	

Issue 101

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Incorrect data from REMODEL.	The REMODEL trial reported a statistically significant and clinically meaningful reduction in SNOT-20 scores compared with baseline of **-1.59** for balloon **sinus dilation** and -1.60 for FESS after **12** months.	The value of -1.70 ± 0.98 is not the balloon dilation value reported by Cutler et al at 6 months follow-up. The 12-month values reported by Chandra et al (2016) on the final cohort (n=135) should be used.	Text amended to reflect results of REMODEL trial as reported by Cutler et al. (2013) at 6 months. For the reasons previously described, the EAC believes this study should be used for the shorter term outcomes which were poorly reported or absent in the paper by Chandra et al.

Issue 102

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Not using the most current data.	There was no significant difference in SNOT-20 score compared with FESS at any time point.	Delete the section about the difference at 1 week. This did not hold out statistical significance with the final cohort (Chandra et al, 2016).	To be consistent with our approach, the EAC believes this result should be kept in. 1 week results were only presented graphically in the study by Chandra et al

Issue 103

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Duplicate references.	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**,7,**8**,9,10,12].	As noted previously, reference number 49 is a duplicate of reference 8 and reference 92 is a duplicate of reference 6.	Thank you for highlighting this, the reference has been updated.

Issue 104

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Incorrect data used.	The REMODEL study did report the mean number of postprocedure debridements per patient was statistically significantly lower in the balloon arm compared to FESS (0.2 vs 1.0, p<0.0001) [4]	The Chandra paper is referenced, but the values provided were those reported by Cutler et al (2014) on the smaller cohort.	The reference has been updated.

Issue 105

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Incorrect data used.	The REMODEL study did report the mean number of postprocedure debridements per patient was statistically significantly lower in the balloon arm compared to FESS (0.2 vs 1.0, p<0.0001) [4]	The Chandra paper is referenced, but the values provided were those reported by Cutler et al (2014) on the smaller cohort.	This issue is a repetition of issue 104.

Issue 106

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Incomplete information.	Additionally, there was 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].	The benefit of reduced nasal bleeding was missing and clarified that the reduced analgesia was specific for prescription medications. Also removed the word “some” to describe the evidence since this is a very subjective term when the data were statistically significant.	The text in the report has been amended.

Issue 107

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Subjective wording.	There is evidence reported on the efficacy of XprESS MSDS when used on different sinuses.	Describing the evidence as limited is subjective. The XprESS Multi-Sinus study was statistically powered to test the study hypothesis at 90% power and enrolled more than the minimum number of participants to meet the sample size requirement for each subgroup except the combination of maxillary and sphenoid sinuses. Therefore, the evidence is from this study is statistically strong. Additionally, although not included within the scope of the clinical	The EAC has changed the wording to “indirect”. The EAC judges it fair to describe the evidence of the sinus comparisons because the evidence came from subgroup analysis of a single armed observational study. Thus, to show comparative efficacy of the XprESS MSDS on individual sinuses with FESS it is necessary to extrapolate this analysis further, meaning the evidence is also indirect. Ideally, to show good evidence of equivalence, prospective comparative

		evidence analysis, multiple studies using the Acclarent Relieva balloon support the findings of the XprESS Multi-Sinus study that balloon dilation is effective in the maxillary, frontal, and sphenoid sinuses.	evidence is required.

Issue 108

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 168: Duplicate reference.	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**].	As noted previously, reference 92 is a duplicate of reference 6.	Thank you for highlighting this, the reference has been updated.

Issue 109

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 169: Outcomes are not applicable to ambulatory balloon dilation.	There was no information reported in the studies on other outcomes defined in the scope, including the procedure duration, and staff required for either procedure.	For the studies presented, outcomes of length of hospital stay and rate of readmission are not applicable. The balloon procedures were primarily conducted as ambulatory procedures under local anaesthesia so there was no hospital stay. The patients were able to leave the office/clinic immediately after the procedure. Likewise, readmission rates were not applicable. Revision surgery	No change, the EAC has factually reported on which outcomes in the scope were addressed.

		and adverse event rates were collected and reported as more relevant outcomes.	

Issue 110

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 159: Subjective wording.	Evidence of the effectiveness of treatment of other than the maxillary and anterior ethmoid sinuses is **provided by a statistically powered observational study [6].**	Describing the evidence as limited is subjective. The XprESS Multi-Sinus study was statistically powered to test the study hypothesis at 90% power and enrolled more than the minimum number of participants to meet the sample size requirement for each subgroup except the combination of maxillary and sphenoid sinuses. Therefore, the evidence is from this study is statistically strong. Additionally, although not included within the scope of the clinical evidence analysis, multiple studies using the Acclarent Relieva balloon support the findings of the XprESS Multi-Sinus study that balloon dilation is effective in the maxillary, frontal, and sphenoid sinuses.	Wording changed to “indirect”, see reply to comment 107.

Issue 111

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 5, page 170: Missing information.	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.	The reduction in nasal bleeding after discharge is an important finding that was not included.	The EAC has amended the text.

Issue 112

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 6, page 171: Outcome that is not applicable to ambulatory balloon dilation.	Furthermore, evidence relating to resource use was limited, with no information pertaining to the duration of surgery with the XprESS MSDS.	Length of hospital stay is not an outcome that is applicable to ambulatory balloon dilation procedures. The benefit of a balloon procedures conducted in an ambulatory setting under local anaesthesia is that there is no postprocedure hospital stay. The patients are able to leave the ambulatory setting after the procedure .compared to FESS where the patient will likely incur an overnight stay after the procedure.	No change, the EAC has factually reported on how the outcomes presented in the scope were addressed.

Issue 113

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 6, page 171: Future study design recommendations are overly burdensome considering the current evidence presented.		The company strongly disagrees with the EAC assessment that another RCT is required to demonstrate efficacy of the device within the NHS. REMODEL was a statistically powered, well-conducted randomized control trial that assessed clinically relevant endpoints at time periods that are considered more than adequate.	No change to the report has been made. The EAC suggests that a study set within the NHS would ideally be a RCT. This is not a factual inaccuracy.