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Sean Carrie,[1,2*] Tony Fouweather,[3] Tara Homer,[3] James O'Hara,[1] Nikki Rousseau,[4] Leila Rooshenas,[5] Alison Bray,[2,6] Deborah D Stocken,[4] Laura Ternent,[3] Katherine Rennie,[7] Emma Clark,[7] Nichola Waugh,[7] Alison J Steel,[7] Jemima Dooley,[8] Michael Drinnan,[2,6] David Hamilton,[3] Kelly Lloyd,[4] Yemi Oluboyede,[3] Caroline Wilson,[5] Quentin Gardiner,[9] Naveed Kara,[10] Sadie Khwaja,[11] Samuel Chee Leong,[12] Sangeeta Maini,[13] Jillian Morrison,[14] Paul Nix,[15] Janet A Wilson[3] and M Dawn Teare[3]

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Abstract

Effectiveness of septoplasty compared to medical management in adults with obstruction associated with a deviated nasal septum: the NAIROS RCT

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Background: The indications for septoplasty are practice-based, rather than evidence-based. In addition, internationally accepted guidelines for the management of nasal obstruction associated with nasal septal deviation are lacking.

Objective: The objective was to determine the clinical effectiveness and cost-effectiveness of septoplasty, with or without turbinate reduction, compared with medical management, in the management of nasal obstruction associated with a deviated nasal septum.

Design: This was a multicentre randomised controlled trial comparing septoplasty, with or without turbinate reduction, with defined medical management; it incorporated a mixed-methods process evaluation and an economic evaluation.

Setting: The trial was set in 17 NHS secondary care hospitals in the UK.

Participants: A total of 378 eligible participants aged > 18 years were recruited.

Interventions: Participants were randomised on a 1: 1 basis and stratified by baseline severity and gender to either (1) septoplasty, with or without turbinate surgery (*n* = 188) or (2) medical management with intranasal steroid spray and saline spray (*n* = 190).

Main outcome measures: The primary outcome was the Sino-nasal Outcome Test-22 items score at 6 months (patient-reported outcome). The secondary outcomes were as follows: patient-reported outcomes – Nasal Obstruction Symptom Evaluation score at 6 and 12 months, Sino-nasal Outcome Test-22 items subscales at 12 months, Double Ordinal Airway Subjective Scale at 6 and 12 months, the Short Form questionnaire-36 items and costs; objective measurements – peak nasal inspiratory flow and rhinospirometry. The number of adverse events experienced was also recorded. A within-trial economic evaluation from an NHS and Personal Social Services perspective estimated the incremental cost per (1) improvement (of ≥ 9 points) in Sino-nasal Outcome Test-22 items score, (2) adverse event avoided and (3) quality-adjusted life-year gained at 12 months. An economic model estimated the incremental cost per quality-adjusted life-year gained at 24 and 36 months. A mixed-methods process evaluation was undertaken to understand/address recruitment issues and examine the acceptability of trial processes and treatment arms.

Results: At the 6-month time point, 307 participants provided primary outcome data (septoplasty, *n* = 152; medical management, *n* = 155). An intention-to-treat analysis revealed a greater and more sustained improvement in the primary outcome measure in the surgical arm. The 6-month mean Sino-nasal Outcome Test-22 items scores were −20.0 points lower (better) for participants randomised to septoplasty than for those randomised to medical management [the score for the septoplasty arm was 19.9 and the score for the medical management arm was 39.5 (95% confidence interval −23.6 to −16.4; $p < 0.0001$)]. This was confirmed by sensitivity analyses and through the analysis of secondary outcomes. Outcomes were statistically significantly related to baseline severity, but not to gender or turbinate reduction. In the surgical and medical management arms, 132 and 95 adverse events occurred, respectively; 14 serious adverse events occurred in the surgical arm and nine in the medical management arm. On average, septoplasty was more costly and more effective in improving Sino-nasal Outcome Test-22 items scores and quality-adjusted life-years than medical management, but incurred a larger number of adverse events. Septoplasty had a 15% probability of being considered cost-effective at 12 months at a £20,000 willingness-to-pay threshold for an additional quality-adjusted life-year. This probability increased to 99% and 100% at 24 and 36 months, respectively.

Limitations: COVID-19 had an impact on participant-facing data collection from March 2020.

Conclusions: Septoplasty, with or without turbinate reduction, is more effective than medical management with a nasal steroid and saline spray. Baseline severity predicts the degree of improvement in symptoms. Septoplasty has a low probability of cost-effectiveness at 12 months, but may be considered cost-effective at 24 months. Future work should focus on developing a septoplasty patient decision aid.

Trial registration: This trial is registered as ISRCTN16168569 and EudraCT 2017-000893-12.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/MVFR4028).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

A&E	accident and emergency
AE	adverse event
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CTIMP	Clinical Trial of an Investigational Medicinal Product
CUA	cost–utility analysis
DMC	Data Monitoring Committee
DOASS	Double Ordinal Airway Subjective Scale
eCRF	electronic case report form
ENT	ear, nose and throat
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GP	general practitioner
HTA	Health Technology Assessment
HUQ	healthcare utilisation questionnaire
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention to treat
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIV	maximal inhalation volume
NAIROS	Nasal AIRway Obstruction Study
NCTU	Newcastle Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NOSE	Nasal Obstruction Symptom Evaluation
NPR	nasal partitioning ratio
NPT	normalisation process theory
PI	principal investigator
PIS	participant information sheet
PNIF	peak nasal inspiratory flow
PPI	patient and public involvement
PROM	patient-reported outcome measure
PSS	Personal Social Services
QALY	quality-adjusted life-year
QRI	Qualitative research integrated within Trials Recruitment Intervention
QuinteT	Qualitative research integrated within Trials
R	recruiter
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-36	Short Form questionnaire-36 items
SNOT-22	Sino-nasal Outcome Test-22 items
STEPP	subpopulation treatment effect pattern plot
SUR	seemingly unrelated regression
TMG	Trial Management Group
TSC	Trial Steering Committee

Plain language summary

Septoplasty is an operation to straighten the septum, which is the partition wall between the nostrils inside the nose. Septoplasty can be used as a treatment for people who have a bent septum and symptoms of a blocked nose, such as difficulty sleeping and exercising. Medical management (a saltwater spray to clear the nose followed by a nose steroid spray) is an alternative treatment to septoplasty. The Nasal AIRway Obstruction Study (NAIROS) aimed to find out whether septoplasty or medical management is a better treatment for people with a bent septum and symptoms of a blocked nose. We recruited 378 patients with at least moderately severe nose symptoms from 17 hospitals in England, Scotland and Wales to take part in the NAIROS. Participants were randomly put into one of two groups: septoplasty or medical management.

Participants' nose symptoms were measured both when they joined the study and after 6 months, using a questionnaire called the Sino-nasal Outcome Test-22 items. This questionnaire was chosen because patients reported that it included symptoms that were important to them. Other studies have shown that a 9-point change in the Sino-nasal Outcome Test-22 items score is significant. After 6 months, on average, people in the septoplasty group improved by 25 points, whereas people in the medical management group improved by 5 points. We saw improvement after septoplasty among patients with moderate symptoms, and among those with severe symptoms. Most patients who we spoke to after a septoplasty were happy with their treatment, but some would have liked more information about what to expect after their nose surgery. In the short term, septoplasty is more costly than medical management. However, over the longer term, taking into account all the costs and benefits of treatment, suggests that septoplasty would be considered good value for money for the NHS.

Scientific summary

Background

The indications for septoplasty are practice-based, rather than evidence-based. In addition, internationally accepted guidelines for the management of nasal obstruction associated with nasal septal deviation are lacking.

Objectives

The study objectives are split into three different aspects: clinical effectiveness, economic evaluation and mixed-methods process evaluation.

Objective 1 was to measure clinical effectiveness according to:

- subjective self-reported rating of nasal airway obstruction
- heterogeneity of estimated treatment effect, specifically according to severity of obstruction and gender
- objective measures of nasal patency
- number of adverse events (AEs) and additional interventions required
- technical failure in the surgical arm
- how well those agreeing to enter the trial reflect those screened for eligibility.

Objective 2 was to conduct an economic evaluation from the perspective of the NHS and Personal Social Services. This entailed the following processes:

- conducting a cost-effectiveness analysis, with outcomes reported as incremental cost per ≥ 9-point improvement in the Sino-nasal Outcome Test-22 items (SNOT-22) scores and number of AEs
- conducting a cost–utility analysis, with outcomes reported as incremental cost per quality-adjusted life-year (QALY) gained
- designing a longer-term economic model to assess costs and health consequences beyond the 12-month follow-up period.

Objective 3 was to conduct a mixed-methods process evaluation of the trial and interventions, to understand:

- barriers to optimal recruitment, and potential solutions to address these, through integration of the Qualitative research integrated within Trials (QuinteT) Recruitment Intervention (QRI)
- participants' and healthcare professionals' experiences of trial participation and the interventions, and perceived factors likely to influence wider implementation of trial findings.

Methods

The Nasal AIRway Obstruction Study (NAIROS) was a multicentre, non-blinded randomised controlled trial comparing the effectiveness of septoplasty, with or without turbinate surgery, with a standardised medical management package of 6 months of intranasal steroid spray and saline spray. Participants were randomised on a 1 : 1 basis between the septoplasty (within 8 weeks) and medical management arms. The trial included an integrated health economic evaluation and a mixed-methods process evaluation incorporating a QRI.

The target sample size of 378 participants allowed for 20% dropout to deliver 90% power for detecting a minimal clinically important difference of 9 points in SNOT-22 scores. This assumed a two-sided type error rate of 5% and a standard deviation of 24 points in SNOT-22 scores at 6 months.

Interventions

The two interventions being compared were as follows.

1. Septoplasty, with or without inferior turbinate reduction in the contralateral nostril, performed at the discretion of the investigating clinician, preferably performed within 8 weeks of randomisation or, if not, by 12 weeks.
2. Medical management with 6 months of mometasone furoate 50 µg per dose nasal steroid spray, suspension (Nasonex®; Merck Sharp & Dohme Limited, Hoddesdon, UK), and isotonic nasal saline spray. Participants had the option of deferred surgery after 6 or 12 months post randomisation.

Setting and participants

We recruited 378 patients to the main trial from 17 NHS hospitals in Great Britain. Eligible patients were identified from general ear, nose and throat referrals. Of those recruited, 188 were randomised to septoplasty and 190 were randomised to medical management.

Inclusion criteria

- Adults aged ≥ 18 years.
- Baseline Nasal Obstruction Symptom Evaluation (NOSE) scale score of ≥ 30.
- Septal deflection visible via nasoendoscopy.
- Capacity to provide informed consent/complete trial questionnaires.

Exclusion criteria

- Prior septal surgery.
- Systemic inflammatory disease/use of oral steroid treatment in the previous 2 weeks.
- Granulomatosis with polyangiitis.
- Nasoendoscopic evidence of unrelated associated pathology.
- Intranasal recreational drug use in the previous 6 months.
- Breastfeeding, pregnancy or intended pregnancy for duration of involvement in the trial.
- Bleeding diathesis.
- Therapeutic anticoagulation.
- Contraindication to general anaesthesia.
- Immunocompromised.
- External bony deformity.

Measurement of clinical outcomes

Primary outcome

The primary outcome was patient-reported assessment of nasal and general symptoms, using the SNOT-22 questionnaire, at 6 months (−2 weeks/+4 weeks). The SNOT-22 was also assessed at baseline and 12 months (± 2 weeks).

Secondary outcomes

- Objective measures: peak nasal inspiratory flow and rhinospirometry (maximal inhalation volume and tidal breathing) at baseline and at 6 and 12 months.
- Patient-reported outcomes: SNOT-22 subscales at 12 months, NOSE score and Double Ordinal Airway Subjective Scale at baseline and at 6 and 12 months.

- Safety measures: number and characteristics of any AEs, surgical complications and reinterventions within 12 months.
- Quality of life, measured using the Short Form questionnaire-36 items (SF-36) at baseline and at 6 and 12 months.
- Healthcare utilisation questionnaire at baseline and at 6 and 12 months.
- Time and travel questionnaire at 12 months.

Measurement of health economic outcomes

- To compare costs incurred by the NHS and Personal Social Services (PSS) with those incurred by participants in the management of a deviated septum.
- To compare QALYs, based on responses to the SF-36 administered at baseline and at 6 and 12 months, converted to Short Form questionnaire-6 Dimensions (SF-6D) utility scores, derived using the area under the curve method.
- To compare the cost-effectiveness of septoplasty with that of medical management at 12 months, measured in terms of the incremental:
    - cost per improvement (of ≥ 9 points) in SNOT-22 scores
    - cost per AE avoided
    - cost per QALY gained.
- To compare the cost-effectiveness of septoplasty with that of medical management at 24 and 36 months in terms of the incremental cost per QALY gained (costs and QALYs were extrapolated using an economic model).

Mixed-methods process evaluation outcomes

The objectives for the mixed-methods process evaluation were addressed through observations of training and NAIROS meetings, interviews with health professionals and participants, audio-recording of recruitment discussions and review of screening logs.

The QRI initiated with a 'pre-recruitment' phase to raise awareness about common recruitment issues/solutions learnt from previous trials. Phase 1 of the QRI investigated sources of recruitment difficulty that were specific to the NAIROS, informing 'actions' to optimise recruitment as the trial was under way (phase 2).

Statistical analysis

The primary statistical analysis was carried out on an intention-to-treat (ITT) basis, retaining patients in their randomised treatment groups. Multivariable linear regression models were used to compare the 6-month SNOT-22 scores between the treatment groups, adjusting any treatment effect by baseline SNOT-22 score and stratification factors at randomisation [(1) gender and (2) severity at baseline (according to three NOSE categories reported in the literature: 30–50, moderate; 55–75, severe; and 80–100, extreme)].

Sensitivity analyses, including a per-treatment and a per-protocol analysis, were also undertaken. Secondary outcomes were analysed in a way that was similar to the primary outcome analysis.

Economic analysis

The cost-effectiveness of septoplasty, compared with medical management, was evaluated by estimating the total costs incurred by the NHS and PSS to manage a deviated septum and averaging these costs across participants in each study arm. Both within-trial and model-based analyses were undertaken. The within-trial analysis estimated costs and effects over 12 months. Three different measures of effects were used: improvement (of ≥ 9 points) in SNOT-22 scores, number of AEs and QALYs.

QALYs were derived from responses to the SF-36, which we converted into SF-6D scores (utilities) using a standardised algorithm and the area under the curve approach. An economic model was designed to extrapolate costs and benefits beyond the 12-month study follow-up period.

Mixed-methods process evaluation analysis

QuinteT Recruitment Intervention: thematic and content analyses were undertaken of interviews and audio-recorded consultations, and descriptive analyses of screening log data were undertaken.

Qualitative process evaluation: a thematic analysis was undertaken using a coding framework, informed by normalisation process theory.

Results

Primary outcomes

The ITT analysis found that, at 6 months, participants randomised to the septoplasty arm (n = 152) had SNOT-22 scores that were, on average, 20.0 points lower (i.e. better) than those of participants randomised to medical management (n = 155) [95% confidence interval (CI) −23.6 to −16.4 points; $p < 0.0001$]. This strong signal was confirmed by both sensitivity analyses and analysis of secondary outcomes. The mean SNOT-22 scores at 6 months were 19.9 points for the septoplasty arm and 39.5 points for the medical management arm. At 12 months, the adjusted mean difference for SNOT-22 scores between the two arms had reduced to −10.1 points (95% CI −14.5 to −5.6 points; $p < 0.0001$). This diminished effect at 12 months was predominantly due to SNOT-22 scores tending to reduce over time among those randomised to medical management. Overall, the improvement in SNOT-22 score in the surgical arm was both notably faster and greater, and was sustained over the trial period. Increased baseline severity of nasal obstruction was associated with greater improvements in the primary outcome. Gender had no impact on outcome improvement. Approximately 45 out of 190 (24%) participants discontinued allocated medical management treatment and had non-trial surgery, and 22 out of 188 (12%) of those randomised to septoplasty did not receive the surgical intervention. The per-protocol (treatment effect −19.7, 95% CI −23.4 to −16.0) and per-treatment analyses (treatment effect −19.3, 95% CI −23.3 to −15.3) confirmed a statistically significant greater improvement in the surgical arm.

Secondary outcomes

All secondary outcome measures, both patient-reported and objective measures, showed a greater improvement in the surgical arm. Turbinate reduction did not appear to add additional benefit in comparison with septoplasty alone. At 6 months, 80% of patients reported improvement in nasal breathing (74% at 12 months). Six out of 166 patients undergoing septoplasty were recommended to consider revision septoplasty.

Adverse events

Overall, there were 227 AEs: 132 in the surgical arm and 95 in the medical management arm. Fourteen serious adverse events occurred in the surgical arm and nine in the medical arm. At 6 months, 7 out of 174 (4%) participants experienced hospital re-admission with nasal bleeding, none of whom required operative reintervention. Twenty out of 172 (12%) participants reported infection requiring antibiotic treatment, 19 out of 171 (11%) participants reported decreased sense of smell, 18 out of 171 (11%) participants reported numbness of the upper teeth and 17 out of 171 (10%) participants reported change in appearance of the nose. Six nasal septal perforations (3%) and seven intranasal adhesions (4%) were noted at 6 and 12 months' follow-up.

Economic evaluation

On average, septoplasty was more costly and more effective in terms of improvements in SNOT-22 score and QALYs than medical management. The incremental cost per improvement (of ≥ 9 points) in SNOT-22 score was £4855. The incremental cost per QALY gained was £27,114 and septoplasty had a

15% probability of being considered cost-effective at a £20,000 willingness-to-pay threshold for an additional QALY. This probability increased to 68% at a £30,000 threshold. Septoplasty was dominated by medical management when AEs were the outcome of interest, as it was more costly and associated with a greater number of AEs. The economic model estimated the incremental cost per QALY gained at 24 months (£13,221) and 36 months (£7368). Septoplasty had a 99% (at 24 months) and a 100% (at 36 months) probability of being considered cost-effective, compared with medical management, at a £20,000 threshold for an additional QALY.

Mixed-methods process evaluation

QuinteT Recruitment Intervention findings

Data sources included 19 interviews with recruiters, 108 audio-recorded discussions and regular scrutiny of screening logs. Despite recruiters' commitment to the NAIROS, there were challenges operationalising recruitment processes into routine clinical care, which restricted identification of potentially eligible patients. Analysis of recorded consultations revealed evidence of recruiters operationalising the pre-recruitment training, but also illuminated unanticipated challenges around explaining the trial arms, which undermined equipoise. Tailored actions were implemented in phase 2 to address these issues, through feedback/training for individuals/groups, 'recruitment workshops' with sites, and written guidance and webinars for professionals who interacted with patients throughout the clinical pathway. The recruitment target was reached successfully without a funding extension and without the need to open additional sites.

Qualitative process evaluation

Nine surgeons and five research nurses working on the NAIROS trial were interviewed and 39 interviews were conducted with 31 participants. Prior to the NAIROS, decisions regarding the appropriateness of surgery for individual patients were made on the basis of a complex and largely subjective combination of symptoms, history and patient anatomy. Surgeons indicated that they would welcome clearer criteria to guide decision-making. However, although some surgeons embraced a role for standardised outcome measures such as the NOSE and the SNOT-22 in decision-making, others were more reluctant; this could be a barrier to the implementation of trial findings.

Although trial findings show that, as a group, participants in the surgical arm experienced more improvement than those in the medical management arm, the qualitative study demonstrated that individual experiences were varied. Although some patients in the medical management arm achieved little or no benefit from treatment, others did report positive effects, with a possible mechanism of action being a reduction in turbinate size. Patients undergoing medical management might benefit from individual advice regarding application of the sprays, taking into account distorted anatomy, to maximise effectiveness and reduce side effects. Although most participants were able to incorporate spray use into their daily routines, long-term spray use was perceived by some to be burdensome.

Despite the large number of participants who perceived septoplasty to be effective in reducing their symptoms, there were still some participants who felt that they received little to no benefit from the operation. Participants reported being underprepared for the immediate post-surgery period.

Limitations

COVID-19 had a major impact on the study, resulting in the cessation of clinical measurements and objective outcomes from March 2020. From that time, all patient-reported outcomes were collected by post or online, or transcribed over the telephone. The ITT analysis is likely to offer an overestimate of the true impact of medical management in improving outcomes as 22% of participants in that arm received septoplasty before the 12-month outcome point.

Conclusions

Septoplasty, with or without turbinate reduction, is a clinically effective intervention. Participants with a deviated nasal septum with a moderate, severe or extreme baseline severity of nasal obstruction symptoms had an improvement in patient-reported outcomes at 6 and 12 months. This improvement surpassed that of standardised medical management. The results suggest that surgery has a low probability of being cost-effective at 12 months but may be considered cost-effective at 24 months.

Impact on health services

The NAIROS clearly demonstrates that adults presenting with nasal obstruction associated with a deviated nasal septum, in the absence of clinical evidence of a coexistent nasal/sinus disease and with a baseline NOSE score of > 30, can reliably be offered surgery in the knowledge that improvements in patient-reported outcomes are superior to improvements when treated with a nasal steroid/saline spray combination.

Recommendations for research

- The most important research priority to emerge from the NAIROS is the need to develop a patient decision aid to explore management of a deviated nasal septum.
- The place of medical treatment in the management of nasal obstruction associated with a deviated nasal septum needs to be explored further.
- A prospective randomised trial would be required to examine the place of turbinate reduction surgery in nasal obstruction.

Study registration

This trial is registered as ISRCTN16168569 and EudraCT 2017-000893-12.

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Chapter 1 Introduction

Scientific background

The Nasal AIRway Obstruction Study (NAIROS) addresses the clinical effectiveness and cost-effectiveness of the operative procedure septoplasty in patients aged > 18 years who have symptoms of nasal obstruction in the presence of a deviated nasal septum. Septoplasty is a commonly performed operation to straighten the mid-line partition between the two nostrils. Within the bony nasal cavities, the lateral aspects (internal sidewalls) each have three nasal turbinates. These are bony structures rich in vascular and glandular tissue projecting into the nasal cavity, which are affected by variable swelling and glandular oversecretion among those with either allergic or non-allergic rhinitis (swelling of nasal cavity lining). The largest and most accessible of those is the inferior turbinate (which is lowest on the sidewall). In addition, when there is a septal deviation, a space is created in the wider nostril, and the inferior turbinate can expand into this space.[1]

Many septal operations are combined with reduction of one or both of the inferior turbinates.[2] Turbinate reduction is performed on the assumption that an increase in nasal airway volume will facilitate better functional nasal airflow, which will in turn improve patient symptoms.[3] However, the evidence base for this is limited. In 2007, there were around 95,000 septoplasties performed in Germany[4] and around 132,000 turbinate reductions, equating to 1% of all operations in Germany that year. In the USA, > 250,000 septal operations are performed annually.[5] Over a 12-month period in 2019/20, approximately 16,700 septoplasty procedures were performed in England,[6] at a cost of £15.9M.

Nasal septal deviation can be either congenital or acquired.[7] Septal deformities may arise in early fetal development. Ruano-Gil *et al.*[8] noted septal deformities in 4% of 50 fetuses before any intrauterine compressive forces could act, suggesting a possible underlying hereditary factor. Overall, the most common cause of septal deviation is trauma, which can occur at any stage of life. The index injury may not be recollected; for example, in childhood, a fall as a toddler can lead to unrecognised septal trauma. In adulthood, sporting injuries or assault are commonly reported causes of septal deviation. Increasing age and male sex are also associated with a higher prevalence of septal deviation.[9]

Septal deflection may cause cosmetic nasal abnormalities. However, the main, functional problems are those related to nasal obstruction: that is, snoring and sleep-disordered breathing. Nasal obstruction is reported in up to 80% of patients and is the nasal symptom most commonly presenting to otolaryngologists.[10] Nasal obstruction was also found to affect one in four of the Swedish population.[11] A significant proportion of nasal obstruction is due to rhinitis, which affects almost 20% of the European population.[12] It is both a poorly understood and poorly characterised symptom: in reality, many patients with a grossly deviated septum do not report symptoms of obstruction, whereas others, with minimal deviation, do. Nasal obstruction has been shown to increase resistance in the upper airways, thus contributing to snoring and sleep apnoea, for which patients, often prompted by their partner, seek treatment.[13] Despite the relationship between nasal obstruction and obstructive sleep apnoea, the impact of surgery in improving nasal patency remains uncertain.[14] In a small randomised controlled trial (RCT), Koutsourelakis *et al.*[15] found that septoplasty rarely treats obstructive sleep apnoea effectively. In contrast, another small study showed that septoplasty did improve patient-related outcomes concerning difficulty falling asleep and awakening at night.[16]

The anterior nasal septum is a cartilaginous structure, never geometrically straight. Researchers have varyingly estimated the prevalence of deviation from 22% to > 70%, reflecting the lack of accepted definition or measurement of what actually constitutes a septal deviation.[7,17] Even estimates from radiological studies range from 20 to > 80%.[18,19] In addition, many nasal conditions other than deviated

nasal septum, such as allergic rhinitis and chronic rhinosinusitis, present with a blocked nose. As part of routine clinical assessment of patients with nasal obstruction, these conditions must be excluded. In practice, in the absence of clinical guidelines in the UK, a clinician's subjective naked-eye assessment of the degree of deviation underpins the decision-making for septoplasty. As a result, decision-making for surgery is subject to great variability and bias.

Studies suggest that anterior septal deviations are more likely to be associated with nasal obstruction than posterior nasal deviations[10] (*Figure 1*). A combination of clinical assessment and fluid dynamic modelling in a 10 year retrospective study showed anterior deflections benefit most from septal surgery.[20] Location is ideally measured with cross-sectional imaging,[21] but cost and radiation exposure preclude its routine use. In one cohort, however, computerised tomography scanning was found to alter the surgical plan in 8% of patients.[22] Evidence confirms that the level of the inferior turbinate is the site that determines the sensation of nasal resistance.[23,24] Cole *et al.*,[25] simulated nasal septal deviations in healthy adults and found that in the majority of adults, the mid and posterior nasal cavities are unresponsive to nasal septal deviation and mucosal changes, but in contrast, that the anterior part of the nose is sensitive to induced septal deviation of as little as 1 mm. The addition of what is called Cottle's manoeuvre, where the patient pulls the cheek away from the obstructed nostril and derives symptomatic benefit, does not appear to add to the specificity of clinical examination.[26]

Headlight illumination allows the first 1–2 cm of septum to be visualised. Septal deviation behind this point requires a nasal endoscopy to assess the mid- and posterior septum and to rule out other pathologies, such as nasal polyps associated with rhinosinusitis.[27] There are fundamental challenges in assessing symptoms of nasal obstruction. In all (except aquatic) mammals under normal circumstances, nasal airflow is greater in one nostril than the other owing to cyclical swelling in the nasal lining (this is known as the 'nasal cycle'). As a result, over a period of 1–4 hours, each nostril exhibits a periodicity of reducing and then increasing resistance, producing a sensation of alternating blockage in each nostril. Therefore, the sensation of nasal obstruction within each nostril is not a 'fixed' phenomenon.[28]

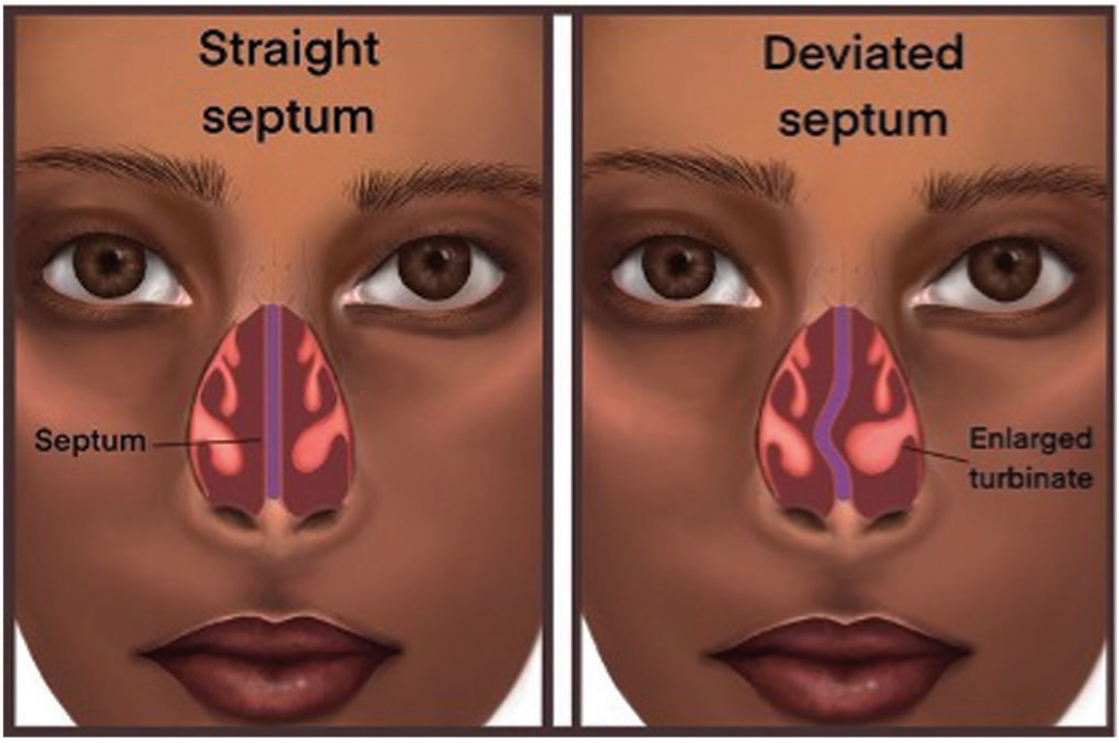

FIGURE 1 Typical appearance associated with a deviated nasal septum nasal obstruction, with compensatory enlargement of the inferior turbinate causing nasal obstruction. ©Frances Grierson, 2021.

Role of the turbinate

Turbinate size has an impact on the volume of the nasal cavity and is influenced by factors such as environmental temperature and humidity, airborne allergens, and respiratory infections such as the common cold. All cyclical swelling within the turbinate contributes to the 'nasal cycle'. In their classification of turbinate enlargement, Hol and Huizing[29] noted compensatory turbinate enlargement in the nostril opposite the side into which the septum is deviated. This so-called compensatory enlargement tends to develop in turbinate tissue exposed to the wider of the two nasal passages[30] (see *Figure 1*). The diagnosis of an enlarged turbinate requires a subjective clinical assessment, and it may simply serve as a diagnosis of exclusion when no other factors are contributing to a blocked nose.

In the UK, patients with nasal obstruction symptoms typically initially self-medicate with nasal decongestants or oral antihistamines. Discussions with pharmacists may lead to the patient commencing a nasal steroid spray. Failure of initial treatments may encourage the patient to seek further options from primary care. Most UK clinical commissioning guidelines will guide general practitioners (GPs) to recommend a trial of intranasal steroid or an alternative steroid medical therapy before considering referral to secondary care for treatment failures, even for those in whom an obviously deviated septum is noted.[31] There is limited scope to undertake visual assessment of the nasal cavity outside secondary care, and there may be alternative or coexistent pathologies, such as allergic rhinitis or chronic rhinosinusitis, contributing to the symptoms of nasal obstruction. Objective assessments of nasal airflow and radiological imaging are rarely undertaken in the UK setting for patients with a deviated nasal septum, although some authorities have long regarded them as useful adjuncts in clinical decision-making.[32,33]

Subjective assessment

The NAIROS used the most commonly employed patient-reported outcome measures (PROMs) in rhinological practice: the Nasal Obstruction Symptom Evaluation (NOSE) scale and the Sino-nasal Outcome Test-22 items (SNOT-22). The NOSE scale was specifically developed as an outcome tool for septoplasty.[34] The five standard NOSE scale items are scored 0–4, that is the total score equals 20. Conventionally, the score is multiplied by five, such that the maximum possible score is converted to 100. A systematic review of postoperative NOSE scale data of 643 patients undergoing a variety of surgical procedures showed an overall weighted mean change of 42 of 100 scaled points.[35] Lipan and Most[36] performed a receiver operating characteristic analysis of NOSE scores obtained in a heterogeneous population of 345 patients undergoing nasal surgery. They defined a NOSE score of < 30 (0–25) as 'mild', 30–50 as 'moderate', 55–75 as 'severe' and 80–100 as 'extreme'. Only 6% of the study population had mild symptoms. For the NAIROS, we predicted that, as with most interventions, baseline severity is the most important determinant of outcome, that is the effect demonstrated would depend on the severity of disease in the sample studied. On the basis of Lipan and Most's[36] receiver operating characteristic findings, those with a NOSE score of < 30 were considered too mildly affected for inclusion in the NAIROS, as similar NOSE scores are reported by patients who do not have nasal obstruction.

The NAIROS randomisation stratified participants according to baseline severity and gender. The decision to reduce the size of the turbinate in the wider of the two nasal passages (unilateral reduction) in the NAIROS was recorded at baseline and was based on the individual ear, nose and throat (ENT) surgeon's assessment of the contribution it made, in combination with the septal deviation, to the symptom of obstruction in any given patient. The NAIROS tested, as a secondary statistical analysis, the contribution of turbinate reduction to any improvement in the nasal airway, an outcome on which published results are inconclusive. Indeed, one study concluded that turbinate reduction alone could be superior to operations involving septoplasty.[2] Gender influences patient responses on the SNOT-22.[37] There are more septoplasties among males,[38] in part at least because of the circumstances surrounding nasal injury. There are anatomical differences in the size and strength of nasal tissue during growth,

which may affect response to surgery.[39] An early study of septoplasty outcome found that only female gender and history of previous nasal surgery were significant predictors of (worse) outcome,[40] but the total evidence base is ambiguous.[41]

The NAIROS measured the SNOT-22 score at baseline (before treatment), at 6 months and at 12 months, with the 6-month SNOT-22 score reported as the primary outcome measure. The SNOT-22 was first applied to septoplasty in 2003,[42] with a mean drop of 16 points from baseline (mean 32 points) 3 months after septal surgery. The SNOT-22 subscale of nasal symptoms reduced from 14 to 7 points, and general health symptoms reduced from 22 to 12 points. A larger study of 126 patients found a smaller reduction of just 4 points at 6 months, perhaps because of a lower starting baseline (mean 22 points).[43]

The mean SNOT-22 score in a UK study of > 2000 patients undergoing surgery for chronic rhinosinusitis was (predictably, given its origins) measured > 44 points preoperatively, with a drop of 30 points, on average, postoperatively.[44] The minimal clinically important difference (MCID) for the SNOT-22 among patients undergoing surgery for nasal polyposis and chronic rhinosinusitis was 8.9 points. In other words, a change of < 9 points on the SNOT-22 was not judged to be a meaningful improvement by the patient. The NAIROS uses a reduction of 9 points as the MCID for the SNOT-22 primary outcome.[43,45–47]

Potentially the most straightforward way of measuring nasal obstruction secondary to a deviated septum is to request that the patient complete a visual analogue scale to quantify the degree of blockage. However, this is a potentially flawed approach, as patients with long-standing septal deviation may become accustomed to breathing with limited nasal airflow.[48] Boyce and Eccles[49] developed the Double Ordinal Airway Subjective Scale (DOASS) as an improvement in the subjective assessment of nasal obstruction. The patient rates the nasal airflow through each nostril independently (with the opposite closed) and characterises the amount of flow on a scale of 1–10, on which 1 is complete blockage and 10 is air flowing freely through the nostril. The DOASS was noted to have a sensitivity of 81% and specificity of 61%, the latter being considerably better than an assessment by visual analogue scale of nasal obstruction.

Objective assessment of the nasal airway

A number of tools have been developed to assess nasal airflow. Rhinomanometry, which measures nasal airway resistance as a function of nasal airflow and the pressure required to create that flow, has been described as the gold standard of assessment.[50] However, it is both cumbersome and time-consuming, and thus impractical from a routine clinical perspective. It may have an advantage over subjective sensation, however, when assessing subtle differences between the two nostrils.[51] Acoustic rhinometry calculates the cross-sectional area of the nasal cavity by measuring the reflection of acoustic pulses introduced into the nostril. Although straightforward to use, it has significant limitations related to the inherent challenges of assessing the physical properties of sound transmission of air in a complex chamber such as the nasal cavity.[52]

The NAIROS used two objective assessments of nasal airflow: rhinospirometry and peak nasal inspiratory flow (PNIF). Rhinospirometry measures the flow and volume of air through each nostril independently.[53] In the NAIROS, it was used to measure both maximal inhalation volume (MIV) and tidal breathing. Asymmetry of nasal airflow is expressed as a nasal partitioning ratio (NPR), calculated as follows: (VL – VR) / (VL + VR), where VL is left-sided volume and VR is right-sided volume. NPR scores range from −1 (complete left nasal cavity obstruction) to 1 (complete right nasal cavity obstruction), with 0 indicating symmetry of airflow.[54] Cuddihy and Eccles[55] measured the NPR of 31 patients before and after corrective surgery for nasal septal deviation. Those patients who had a NPR beyond the normal range had a greater improvement in subjective nasal obstruction. In addition, and as quoted previously, Boyce and Eccles[56] identified that the DOASS score correlated well with the NPR values obtained in rhinospirometry. PNIF measures the peak flow rate of air through both nostrils during forced inhalation.

PNIF has been shown to respond to septoplasty/turbinectomy and can therefore be used for an overall assessment of nasal airflow impairment.[57]

It was expected that, for the NAIROS, a combination of the subjective and objective airway assessments would enable us to construct a robust algorithm for use at baseline to predict which patients were most likely to benefit from septoplasty.

Rationale

The NHS currently purchases 17,000 surgical interventions on the nasal septum across the UK annually, yet the procedure is almost entirely lacking in a suitable evidence base or even adequate guidance. The NHS and personal costs of this practice are considerable and there is an urgent need for evaluation in a substantive study, which, with sufficient sample size and power, has the potential to influence clinical practice, patient choice and NHS commissioning.

Evidence review of septoplasty effectiveness

To our knowledge, van Egmond *et al.*,[58] published the only RCT on the clinical effectiveness of septoplasty in 2019. This study was based on analysis of septal surgery, compared with non-surgical management, across 206 patients in the Netherlands. They concluded that septoplasty was more effective than non-surgical management for nasal obstruction. Those patients randomised to non-surgical management did not receive a standardised treatment, and they received a variety of medical interventions considered appropriate by the treating clinician. Therefore, it is difficult to conclude whether or not a positive trial is the result of an effective intervention or low-efficacy standard care.[59] Furthermore, the primary outcome measure of the trial, the Glasgow Health Status Inventory, a health-related quality-of-life measure, demonstrated an improved score among those patients undergoing surgery. However, the Glasgow Health Status Inventory is known to have limited sensitivity to septal surgery outcomes,[60] and, when compared with the pragmatic medical treatment comparator undertaken by van Egmond *et al.*,[58] this effect may have been exacerbated. Over 75% of the surgical cohort underwent concomitant inferior turbinate surgery, bilateral in 67% of patients, even though inferior turbinate enlargement was noted in < 50% of patients at baseline. This additional surgery is likely to exaggerate the beneficial impact of turbinate surgery over septoplasty alone.[2] In addition, there was a 30% crossover from the non-surgical to the surgical arm, introducing a further potential element of bias or dilution of the full effect of septoplasty.

In a 2018 systematic review of the evidence for septoplasty with or without inferior turbinate reduction as a treatment for nasal obstruction, van Egmond *et al.*[61] first compared septoplasty (with or without concurrent turbinate surgery) with non-surgical management and, second, compared septoplasty alone with septoplasty with turbinate surgery. In their review, there were no RCTs comparing septoplasty with non-surgical management, and five RCTs and six controlled trials comparing septoplasty alone with septoplasty with turbinate surgery. Included studies demonstrated substantial heterogeneity in study population, outcomes measured and time points of outcome assessment. The risk of bias was considered high in most reports. However, although subjective and objective assessment improvements did not necessarily mirror one another, studies demonstrated an overall improvement in nasal obstruction symptom. No additional benefit of turbinate surgery was reported in 8 out of 9 studies using subjective assessments, and 5 out of 7 studies using objective measures. Complications were rare, and were reported in only three studies. There were significant limitations related to short follow-up periods, which in some cases were only 9 months.

In a second systematic review of septoplasty alone, Tsang *et al.*[62] found six studies assessing patient satisfaction; rates varied from 69% to 100% in three studies in which patients were asked if they were satisfied or dissatisfied with outcomes at 6 months. Two studies assessed the degree of patient satisfaction, with one study indicating that 88% of patients were moderately satisfied or better at 1 year

post operation, and the other reporting that 50% of patients were satisfied at 5 years post operation. There was significant heterogeneity in the method of assessment of nasal obstruction, which may have led to the finding that, in general, patients with more severe symptoms of nasal obstruction had a better outcome. The authors noted that there were high risks of bias as studies were only observational, with significant variation across multiple categories including patient population, outcome measures and follow-up duration. Overall, the authors concluded that there was insufficient evidence that septoplasty alone had good long-term patient-reported outcomes in the management of septal deviation, based on the heterogeneity of existing data and lack of RCTs. They recommended further research to define which preoperative characteristics are predictive of both subjectively and objectively positive septoplasty outcomes. Neither systematic review undertook a meta-analysis because of the substantial heterogeneity across the studies included.

Benefits and harms of interventions

Surgical

Septoplasty has level III evidence of effectiveness, and observational studies confirm good levels of patient satisfaction. The operation, if successful, requires a single procedure without the requirement of ongoing medical therapy. However, there is variation in criteria for surgery, surgical technique and postoperative follow-up. Selection criteria for surgery variance was discussed previously, but there is also variance in operative techniques among surgeons and the need for patient follow-up postoperatively. In addition, there is no good-quality evidence on either the clinical effectiveness or the cost-effectiveness of such surgery. Septal surgery also carries an economic cost, in terms of time off work or normal duties, and can be associated with side effects or complications that delay recovery and potentially necessitate additional treatment.

Following surgery, it is normal to have some symptoms, lasting between 48 and 72 hours, of minor bleeding, congestion and nasal discomfort. In our own group's early publication[63] of the outcomes among 121 septoplasty patients at 6 weeks, two postoperative complications were noted: septal perforation (1.7%) and nasal septal adhesions (3.3%). A Chinese study of 54 patients reported nasal septal adhesions in > 7% of patients.[64] Adhesions and septal haematoma may necessitate re-admission for corrective surgery. In addition, minor cosmetic change occurs in up to 30% of patients and more major change in > 4% of patients.[65] Dabrowska *et al.*,[66] in a retrospective series of 5639 patients undergoing septoplasty with or without turbinate reduction, reported excessive bleeding in 3.3%, septal perforation in 2.3%, infection (prolonged healing) in 3.1%, reduced smell acuity in 3.1% and dental anaesthesia in 0.1% of patients.

Septoplasty is routinely performed under general anaesthesia as a day-case procedure. An initial incision is made on one side of the septal lining allowing for the straightening or removal of areas of twisted cartilage and bone. It may not be possible to fully straighten the septum without risking the cosmetic appearance of the nose; therefore, the surgeon must use careful judgement to minimise this risk. The procedure typically takes between 45 and 60 minutes to complete. Nasal packing can be used following surgery; in the NAIROS it was not to be undertaken, if possible, because of the associated discomfort to the patient. Instead, suture repair of the septum was to be performed at the end of the procedure, as this seems to have equal efficacy and fewer disadvantages.[67–69]

Medical management

Nasal steroid sprays have potent anti-inflammatory and antiallergic properties, inhibiting the release of inflammatory mediators produced by the nasal lining, thereby reducing swelling and nasal mucus in the nasal passages. Two sprays of 100 µg of mometasone furoate in each nostril twice daily for 6 weeks, followed by 100 µg per day in each nostril, for the remainder of the 6-month treatment period, was chosen based on the maximum recommended standard nasal steroid dose. This spray was identified in patient and public involvement (PPI) discussions with GPs as being restricted by formulary protocols in

primary care, and therefore unlikely to have been prescribed previously. Mometasone is licensed for use among patients with reduced nasal airway and has marketing authorisation in the UK.

Medical therapy has the obvious advantage of the avoidance of general anaesthesia and surgery and their associated risks. Nasal steroid sprays are standard treatment for nasal obstruction symptoms and are deliverable in primary care. However, they may not be an effective treatment for patients with a deviated nasal septum[70] and, even when they are, patients may require indefinite medical therapy, with its associated costs. Intranasal steroid sprays also have potential risks to the patient: they can cause nasal bleeding (odds ratio 1.56 in a 2020 systematic review, compared with placebo[71]), crusting, pharyngitis and headache, all of which may affect patient compliance, and there are reports which associate increased intraocular pressure and adrenal suppression with such sprays. Both hypersensitivity and anaphylaxis are rare complications.[72] There are few data comparing different intranasal steroid preparations.[72]

Proprietary saline irrigation of the nasal cavity may be performed with either isotonic or hypertonic solutions.[73] These may either be low-positive pressure (from a spray or pump), or gravity-based pressure (using a container with a nasal spout). Saline nasal irrigations have been recommended in the management of various nasal and sinus mucosal disorders such as chronic sinusitis[74] and allergic rhinitis,[75] although this recommendation is based on mostly low-level evidence. Similarly, saline irrigations have been recommended following endoscopic sinus surgery, but uncertainty remains in the literature around the optimum method of delivery and composition of the saline solution.[73–79] Saline sprays have not been trialled specifically in nasal septal deviation. In consultation with GPs and the PPI group, the Stérimar isotonic spray (Sofibel SAS, Paris, France) was chosen for the NAIROS. Mometasone and Stérimar sprays, in combination with the option of deferred surgery for those in the medical management arm, was noted at initial PPI discussions to be an acceptable alternative to surgery by patients.

Aims and objectives

Primary objectives

The primary objective was to compare the clinical effectiveness of nasal septoplasty (with or without unilateral turbinate reduction) with medical management over a duration of 6 months among adults with a nasal septal deviation who have been referred to otolaryngology outpatient clinics with nasal airway obstruction.

Secondary objectives

The secondary objectives are split into three different aspects: clinical effectiveness, an economic evaluation and a mixed-methods process evaluation.

Clinical effectiveness

We aimed to measure clinical effectiveness according to:

- subjective self-report rating of nasal airway obstruction
- heterogeneity of estimated treatment effect, specifically according to severity of obstruction and gender
- objective measures of nasal patency
- safety profile recording the number of adverse events (AEs) and additional interventions required.

Measuring clinical effectiveness according to the above standards would enable us to:

- adjust the estimate of effectiveness in the light of other baseline covariates: severity of self-reported nasal airway obstruction, gender and concomitant turbinate reduction

- use the results in the surgical arm to explore a possible definition of technical failure in experienced hands, that is experienced surgeons (i.e. consultants or non-consultant career clinicians, but not trainee otolaryngologists)
- assess to what extent trial participants are representative of the total population of participants referred to ENT clinics with nasal obstruction due to a septal deviation.

Economic evaluation

We conducted our economic evaluation by:

- assessing cost-effectiveness measured in terms of the incremental cost per improvement (of ≥ 9 points) in SNOT-22 score and AEs avoided over 12 months
- assessing cost-effectiveness measured in terms of incremental cost per quality-adjusted life-year (QALY) gained [derived from responses to the Short Form questionnaire-36 items (SF-36) converted to Short Form questionnaire-6 Dimensions (SF-6D) scores] over 12 months
- designing a longer-term economic model to assess the costs and QALYs beyond the 12-month follow-up period.

Mixed-methods process evaluation of the trial and interventions

Our mixed-methods process evaluation was to identify, describe, understand and address:

- barriers to optimal recruitment, and potential solutions to address these, through integration of the Qualitative research integrated within Trials (QuinteT) Recruitment Intervention (QRI)
- participants' and healthcare professionals' experiences of trial participation and the interventions under evaluation
- factors likely to influence wider implementation of trial findings.

Chapter 2 Methods

Summary of trial design

The NAIROS aimed to establish and inform guidance for the best management strategy for patients with nasal obstruction associated with a deviated septum by comparing a RCT of surgery with medical management.

Adult patients aged ≥ 18 years were identified from referrals to secondary care. Eligible patients who had septal deflection and a NOSE score of ≥ 30 were randomised to the trial. Randomisation occurred on a 1 : 1 basis, and was stratified by gender and severity (i.e. NOSE score) between septoplasty (with or without turbinate reduction), and medical management of combined isotonic saline nasal spray (Stérimar) and mometasone nasal spray.

The target recruitment figure of 378 participants from 17 NHS hospitals was achieved, with recruitment from sites across England, Scotland and Wales. Participants were followed up for 12 months post randomisation. The primary outcome was the total SNOT-22 score measured at 6 months post randomisation.

The trial included a qualitative mixed-methods process evaluation, which included a QRI to optimise recruitment during trial recruitment (see *Chapter 5*), and a qualitative process evaluation about staff and patient participants' experiences of the study (see *Chapter 6*). It also included a full statistical evaluation (see *Chapter 3*) and an economic evaluation (see *Chapter 4*). Further details of the study design, clinical outcomes, economic outcomes and recruitment have been described previously.[80]

Changes to trial design

Feasibility phase

The NAIROS researchers undertook an extensive assessment of the feasibility of the study by triangulating the views of potential patients, GPs and consultant ENT surgeons. This work assessed the willingness of patients to participate in randomisation, clinicians' willingness to refer patients and randomly allocate to trial groups and the acceptability of the deferred surgery treatment arm.

Internal pilot

We originally intended for the NAIROS to include a 5-month internal pilot involving 10 sites. However, delays in study set-up expedited an agreement with the funder to remove the internal pilot and open all 17 sites simultaneously.

The pilot objectives of identifying, understanding and addressing any barriers to recruitment, retention or compliance with protocol were incorporated into the main trial, but extended to the full first year of recruitment. Areas for particular scrutiny during this period included patient recruitment, patient discontinuation of allocated treatment and compliance with surgery window. Monitoring of recruitment, retention and compliance with the protocol continued throughout the whole trial.

Collecting primary and secondary outcome measures

All trial interventions had been administered before the onset of the COVID-19 pandemic in March 2020. Participants in the trial follow-up were invited to complete the PROMs remotely via e-mail or post [i.e. SNOT-22, NOSE, healthcare utilisation questionnaire (HUQ), time and travel questionnaire and SF-36; see *Report Supplementary Material 2*, *4*, *5 and 6*]. The SNOT-22 (primary and secondary outcome measure) could also be completed by participants using a validated online platform hosted by Castor (Castor EDC, Amsterdam, the Netherlands); the method of completion of the SNOT-22 was noted in the database. Owing to suspension of all face-to-face clinic visits from 30 March 2020, no other clinical outcome measure scheduled after this date was collected [i.e. DOASS (see *Report Supplementary Material 3*), clinical examination, symptoms review, measures of nasal patency]. AEs and concomitant medications were collected remotely over telephone at the 6- and 12-month visits from 30 March 2020 until the end of the trial.

Trial registration and protocol availability

The NAIROS was included in the National Institute for Health and Care Research (NIHR) Clinical Research Network portfolio (study number 35368) and was registered on 24 March 2017 [European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2017-000893-12, International Standard Randomised Controlled Trial Number 16168569]. The protocol has been peer reviewed[80] (version 5.0, dated 16 January 2019), and the final protocol version (version 8.0, dated 17 December 2020) is available on the project web page [URL: www.journalslibrary.nihr.ac.uk/programmes/hta/1422607#/ (accessed 30 July 2021)].

Ethics approval and research governance

The trial sponsor was the Newcastle upon Tyne Hospitals NHS Foundation Trust (reference number 08302). Favourable ethics opinion was provided by the North East – Newcastle and North Tyneside 2 UK Health Research Authority Research Ethics Committee (REC) on 31 August 2017 (study reference number 17/NE/0239). The trial received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) (study EudraCT number 2017-000893-12) on 17 August 2017.

Setting

The NAIROS was conducted in the following 17 secondary care hospital trusts in England, Scotland and Wales:

1. NHS Grampian (Aberdeen Royal Infirmary).
2. University Hospitals Birmingham NHS Foundation Trust (Queen Elizabeth Hospital Birmingham).
3. Bradford Teaching Hospitals NHS Foundation Trust (Bradford Royal Infirmary).
4. North Cumbria Integrated Care NHS Foundation Trust (Cumberland Infirmary).
5. County Durham and Darlington NHS Foundation Trust (Darlington Memorial Hospital/University Hospital of North Durham).
6. NHS Tayside (Ninewells Hospital).
7. James Paget University Hospitals NHS Foundation Trust (James Paget University Hospital).
8. NHS Lanarkshire (University Hospital Monklands).
9. Leeds Teaching Hospitals NHS Trust (Leeds General Infirmary).
10. Aintree University Hospitals NHS Foundation Trust (Aintree University Hospital).
11. Guy's and St Thomas' NHS Foundation Trust (Guy's Hospital).
12. Newcastle upon Tyne Hospitals NHS Foundation Trust (Freeman Hospital).
13. Aneurin Bevan University Health Board (Royal Gwent Hospital).

14. University Hospitals Plymouth NHS Trust (Derriford Hospital).
15. Salisbury NHS Foundation Trust (Salisbury District Hospital).
16. Stockport NHS Foundation Trust (Stepping Hill Hospital).
17. Wrightington, Wigan and Leigh NHS Foundation Trust (Royal Albert Edward Infirmary).

Participants

We recruited 378 patients who had a deviated septum and reduced nasal airway (as indicated by a NOSE score of ≥ 30) and had been referred by their GP to ENT secondary care outpatient clinics. They were randomised in all 17 participating centres via dedicated research and standard NHS clinics. We also recruited ENT staff to participate in the process evaluation.

Eligibility criteria

Inclusion criteria

- Adults aged ≥ 18 years.
- Baseline NOSE score of ≥ 30.
- Septal deflection at baseline visible via nasoendoscopy.
- Capacity to provide informed written consent and to complete trial questionnaires.

Exclusion criteria

- Any prior septal surgery.
- Systemic inflammatory disease or the use of oral steroid treatment within the previous 2 weeks.
- Granulomatosis with polyangiitis.
- Nasoendoscopic evidence of unrelated associated pathology, for example adenoid pad, septal perforation, chronic rhinosinusitis indicated by polyposis or pus.
- Any history of intranasal recreational drug use within the previous 6 months.
- Breastfeeding, pregnancy or intended pregnancy for duration of involvement in the trial.
- Bleeding diathesis.
- Therapeutic anticoagulation (warfarin/novel oral anticoagulant therapy).
- Clinically significant contraindication to general anaesthesia.
- Known to be immunocompromised.
- Presence detected of an external bony deformity likely to make a substantial contribution to the nasal obstruction (determined by clinical opinion).

The NOSE score is a validated five-item, unifactorial self-report of nasal-block severity that has been applied in previous research and audit studies.[36,81] The three recognised NOSE-derived categories of baseline severity used were 30–50 (moderate), 55–75 (severe) and 80–100 (extreme). The NAIROS aimed to recruit participants with at least moderate nasal obstruction symptoms.

Intervention

The interventions compared in the RCT were as follows:

- surgical correction (septoplasty) of the nasal septal deviation, with or without unilateral reduction of the contralateral inferior nasal turbinate
- medical management consisting of combined use of a nasal steroid spray and an isotonic saline spray for 6 months.

Delivery of the intervention

Septoplasty

Participants randomised to septoplasty received surgery up to 8 weeks (+ 4 weeks) after randomisation. The additional 4-week window was to allow for extenuating circumstances such as pressure on surgical waiting lists or patient cancellation, with reasons for delays to surgery collected and reported. The NAIROS stipulated that experienced surgeons who were not in training should perform the procedure. They had the option to carry out unilateral turbinate surgery on the wider side, according to their assessment of the individual patient airway. As a pragmatic study, the NAIROS did not ask surgeons to change their usual practice in this regard, reflecting the considerable variation in current UK surgical practice. Both the intention to reduce one turbinate prior to randomisation and details of the actual surgery performed were collected.

Clinical Trial of an Investigational Medicinal Product intervention: medical management

Participants randomised to medical management were supplied with 6 months of Stérimar isotonic nasal saline spray and mometasone furoate nasal steroid spray at the time of randomisation. Use of mometasone, an investigational medicinal product, was as indicated by the marketing authorisation. Twice per day for 6 weeks, each participant sprayed a daily metered Stérimar isotonic nasal saline dose into each nostril, followed by a twice-daily dose of mometasone furoate steroid spray. For the remainder of the 6-month period, the same dose of saline spray applied, and the steroid dose was reduced to 100 µg per day; participants could administer this either by spraying either two 50-µg doses into each nostril once daily or one 50-µg dose into each nostril twice daily.

Discontinuation of allocated treatment

Formal crossovers between trial arms were not permitted, but the NAIROS was designed as a pragmatic RCT; therefore, participants could discontinue allocated treatment and explore other options in standard NHS care while remaining in the trial. Medical management arm participants opting for surgical treatment were invited to defer surgery until after the 12-month follow-up visit and received standard non-trial septoplasty in line with current local waiting times (taking into account the time that they had already spent in the medical management arm). Discontinuation of allocated treatment did not constitute withdrawal from the trial.

Participants randomised to the surgical arm, or medical management participants who wished to continue using nasal sprays beyond the initial 6-month intervention period, could be prescribed mometasone furoate nasal spray and Stérimar isotonic spray (or an alternative at the discretion of the clinician) as per standard practice of the local NHS team and without the need for a NAIROS trial prescription.

Participants who wished to discontinue their allocated treatment but remain in the trial were followed up as scheduled for their allocated arm, with data analysed on an intention-to-treat (ITT) basis.

Funding of the trial intervention

As the surgical intervention was part of the standard pathway of NHS care for this cohort of patients, it was funded from the standard NHS tariff. The 6-month medical management intervention was categorised as an excess treatment cost and was funded by NHS England, Scotland and Wales.

Outcome measurements

Primary outcome

The primary outcome was defined as patient-reported assessment of nasal and general symptoms assessed using the SNOT-22 at 6 months (−2 weeks/+ 4 weeks). The SNOT-22 is scored from 22 questions with each item scored from 0 to 5. The final total score can range from 0 to 110, with a higher score indicating worse symptoms. The SNOT-22 was also assessed at baseline and 12 months.

Secondary outcomes

- Objective assessment: nasal airflow was measured using a PNIF meter and an NV1 rhinospirometer (GM Instruments Ltd, Irvine, UK); both rhinospirometry (i.e. tidal volume and MIV) and PNIF measurements were taken at baseline and at 6 and 12 months. Additional exploratory analysis was undertaken using the rhinospirometer.
- Quality of life was measured using the SF-36 quality-of-life questionnaire (acute/1-week recall) at baseline and at 6 and 12 months.
- Healthcare resource use (primary and secondary care) was measured using a HUQ at baseline and at 6 and 12 months.
- Patient-reported outcome measures: subjective – SNOT-22 subscales (rhinologic, sleep, ear/facial pain, psychological) at 12 months, NOSE scale at baseline and at 6 and 12 months, and DOASS at baseline and at 6 and 12 months were used to measure longer-term outcomes.
- Safety measures: number and characteristics of any AEs and surgical complication/failure and reintervention within 12 months.
- The economic evaluation compared the following between the two intervention arms:
    - costs [the average total cost per participant from the perspective of the NHS and Personal Social Services (PSS)]; sensitivity analyses included participant costs
    - QALYs, based on responses to the SF-36 converted to SF-6D scores, were derived using the area under the curve method[82,83]
    - improvement (of ≥ 9 points) in SNOT-22 scores
    - number of AEs
    - incremental cost per improvement (of ≥ 9 points) in SNOT-22 score
    - incremental cost in number of AEs avoided
    - incremental cost per QALY gained.
- As part of the economic evaluation, costs and effects were extrapolated beyond 12 months using an economic model.

Economic analysis

The NAIROS economic analysis followed a prespecified health economics analysis plan, which outlined the analysis of the NAIROS trial data and aimed to determine the cost-effectiveness of septoplasty, compared with medical management, over 12 months and over a longer time horizon. *Chapter 4* provides detail on the within-trial and longer-term economic models.

Overview of mixed-methods process evaluation

The NAIROS qualitative analysis incorporated the QRI, which aimed to support recruitment and mixed qualitative methods to understand participants' and healthcare professionals' experiences of septoplasty and medical management. The QRI took place throughout recruitment to the NAIROS, using qualitative and novel methods to investigate and address recruitment barriers (see *Chapter 5*). Qualitative interviews and focus groups were conducted throughout the trial to investigate participants' and site staff members' experiences of trial procedures, interventions and barriers to implementing findings into practice (see *Chapter 6*).

Overview of objective outcome measures and analysis

Nasal patency measurement and data collection protocols were devised through review of the scientific literature and the equipment manufacturer's user information (GM Instruments) (see *Report*

Supplementary Material 1), consultation with the NAIROS Trial Management Group (TMG), and consultation with a representative of the manufacturer.

Site staff were trained in these protocols in person during site initiation visits, were provided with a training video[84] and had access to ad hoc support from Northern Medical Physics and Clinical Engineering and GM Instruments.

The NAIROS participants performed two types of objective measures of nasal patency both before and after decongestant: PNIF using a standard device [https://gm-instruments.com/products/nasal-measurements/pnif-meter (accessed 27 August 2021)], and rhinospirometry using an electromechanical/software rhinospirometer device that measured airflow through each nostril independently [https://gm-instruments.com/products/nasal-measurements/nv1-rhinospirometer (accessed 27 August 2021)]. Rhinospirometry was performed during both MIV and tidal breathing. Measurements of nasal patency took place at all three trial visits (baseline and 6 and 12 months post randomisation). End volume (for the rhinospirometer) and flow (for the PNIF meter) values were read from the devices, recorded onto a case report form and then recorded onto the NAIROS database; these parameters are presented and discussed in *Chapter 3*.

Four baseline nasal patency parameters were assessed for potential inclusion in the sensitivity analyses (model 3; see *Sensitivity analyses*).

The four model-3 candidate baseline nasal patency parameters were derived from (1) post-decongestant PNIF and (2) flow rate time series data files saved using the rhinospirometry software, as follows:

1. absolute, post-decongestant, tidal breathing (NPR)
2. the change in absolute NPR following decongestant
3. post-decongestant, tidal breathing tidal volume (both sides combined)
4. post-decongestant, tidal breathing maximum flow rate (both sides combined).

MATLAB® software (version R2019; The MathWorks, Inc., Natick, MA, USA) was used to analyse rhinospirometry data files and extract the four model-3 candidate parameters. Calculations were validated by comparison to values in the manufacturer's rhinospirometer software.

The nasal patency protocols and analyses of rhinospirometry data files to produce the four parameters are described in full in a NAIROS nasal patency measurements report (see *Report Supplementary Material 1*).

Participant timeline

Identification, screening and recruitment of participants

Although primary care clinicians were encouraged to refer patients with a deviated nasal septum directly to nasal research clinics, the majority of eligible patients were proactively identified by researchers from general ENT primary care referrals. Triage of paper referrals and scrutiny of 'choose and book' referrals were used to populate research clinics, or alternatively, research slots in general rhinology/ENT clinics. At the majority of sites, clinicians did not have the resources for dedicated research clinics. Nasal septal deviation can be challenging to diagnose in primary care; therefore, the participants selected to attend research clinics were chosen at the clinicians' judgement.

Screening for study eligibility was maximised by training all staff involved. Potential participants, whenever possible, were sent the participant information sheet (PIS) with their clinic appointment details and were directed to the patient information video available on the trial website.[85] All patients were given a minimum of 24 hours after receiving the PIS to decide whether or not they wished to participate.

Patients were invited to provide written informed consent for the study in three stages, after they had been given sufficient time to consider the trial and had the opportunity to have any questions addressed by the local clinical team.

First, patients were invited to provide consent to undergo screening assessments to determine eligibility for inclusion in the trial.

Eligibility assessments

- Pre-randomisation NOSE scale.
- Age.
- Baseline recording of four core features including endoscopy (without decongestion):
    - the side of the convexity
    - the site of deflection (whether anterior/posterior/upper/lower or all)
    - nasal endoscopy findings to look for evidence of exclusion criteria (e.g. pus/polyps)
    - whether the extent of the observer-rated airway obstruction by the septum was < or > 50% at endoscopy.

Second, patients were invited to provide consent for their discussion about the NAIROS trial to be audio-recorded and for their contact details to be shared with qualitative researchers for a potential telephone interview.

Third, eligible patients were invited to provide consent for the main trial. The following assessments were undertaken only once thereafter.

Assessments pre randomisation

- The SF-36.
- The SNOT-22.
- Measurements of nasal patency pre and post decongestion:
    - PNIF (measured by the PNIF meter)
    - rhinospirometry, allowing calculation of NPR
    - the DOASS (post decongestion only).

Sites were instructed to use xylometazoline hydrochloride (Otrivine Congestion Relief 0.1% Nasal Spray®; GlaxoSmithKline plc, Brentford, UK) nasal spray as the decongestant.

Eligible patients who declined the main trial

To facilitate baseline analysis of the NAIROS trial participants with eligible patients who declined to participate, those in the latter group were invited to provide written consent to collect the following baseline data:

- SNOT-22 score
- NOSE score
- intention to reduce turbinate
- baseline recording of four core features including endoscopy (without decongestion) –
    - the side of the convexity (laterality)
    - the site of deflection (whether anterior/posterior/upper/lower or all)
    - endoscopy findings to look for evidence of exclusion criteria (e.g. pus/polyps)
    - whether the extent of the observer-rated airway blockage by the septum was < or > 50% at endoscopy.

- age
- gender
- reasons for declining.

Screening data, including the number of participants approached, reasons for ineligibility, those interested in taking part and reasons for declining participation, were collected via a log completed by site staff conducting screening. The intention was to compare the NAIROS trial participants to the total pool of those referred at each participating site.

Randomisation

Participant allocation

At the baseline visit, consenting, eligible patients were randomised on a 1: 1 basis using the centrally administered Newcastle Clinical Trials Unit (NCTU) web-based system. Randomisation was by random permuted blocks of variable length, stratified by gender and three recognised NOSE-derived categories of baseline severity as defined previously in *Eligibility criteria*. The treatment allocation was open-label, with the randomisation system providing a unique trial identifier for each participant.

Withdrawal

Participants had the right to withdraw from any element of the RCT at any time without having to give a reason. Participants who withdrew their consent or were withdrawn by the investigator from the trial were not replaced. All data collected until withdrawal were retained for data analysis.

Schedule of events

Participants recruited to the main trial were followed up for 12 months from the point of randomisation (*Figure 2*).

Septoplasty participants

The surgeon's intention to reduce the inferior turbinate was recorded prior to septoplasty and the following information was recorded at the time of surgery:

- the date of surgery
- duration in theatre
- grade of senior surgeon and senior anaesthetist present
- whether septoplasty, with or without unilateral inferior turbinate reduction, was carried out
- technical aspects of the surgery
- discharge medication
- whether or not any complications occurred
- whether or not there was any overnight hospital admission.

Medical management participants

As the NAIROS was a pragmatic trial of standard treatment, formal participant compliance with the medical management intervention was not formally assessed. However, quantities of bottles used per participant and reasons for ceasing treatment were recorded.

Follow-up

Participants were contacted by either telephone, e-mail or text 2 weeks after randomisation (medical management) or 2 weeks after their septoplasty, to record any AEs and concomitant medication. Medical management participants were reminded to reduce their dose of mometasone nasal spray at 6 weeks.

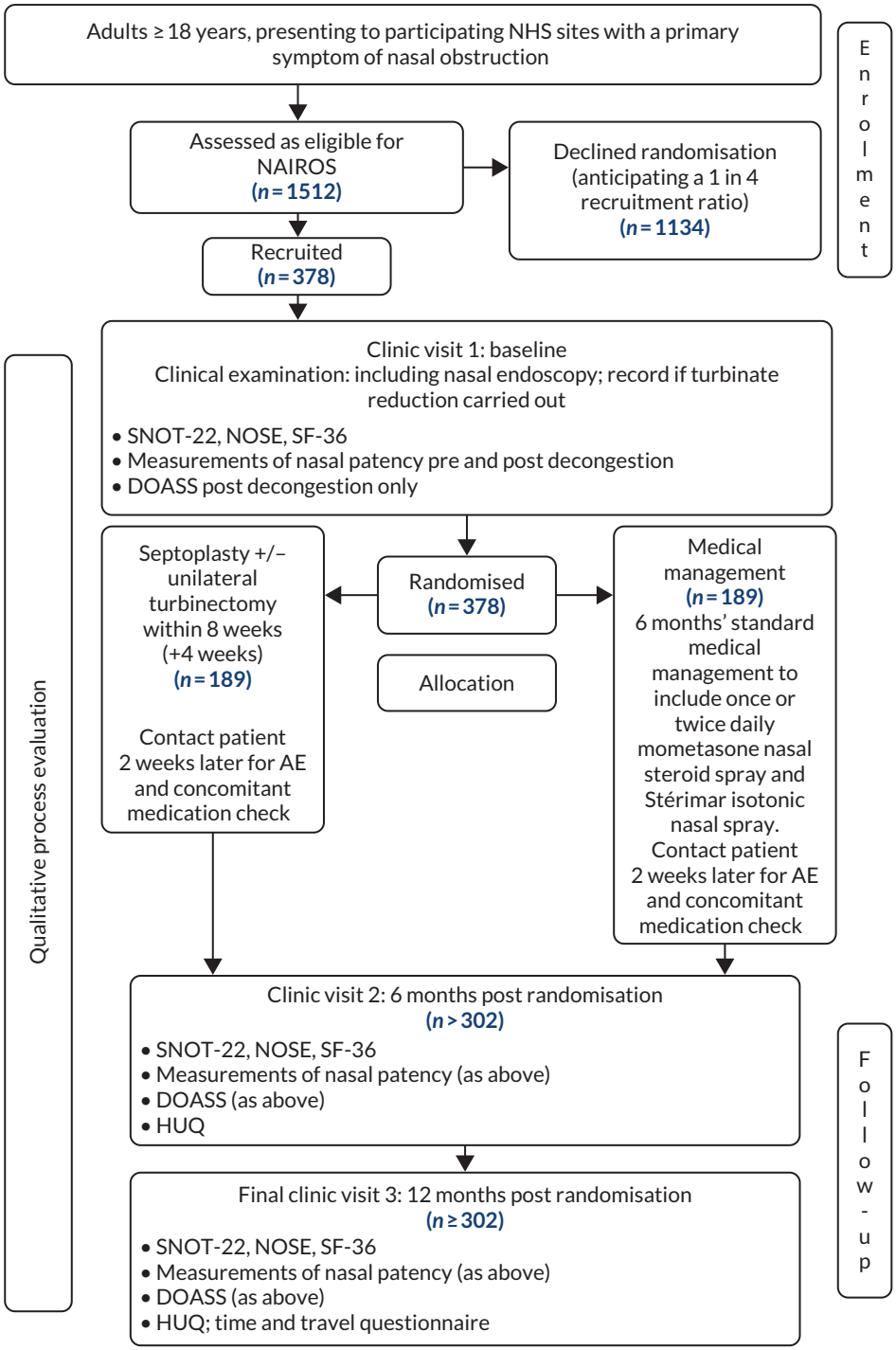

FIGURE 2 The NAIROS participant flow diagram. Reproduced from version 8.0 of the NAIROS protocol (17 December 2020) [see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/1422607#/ (accessed 30 July 2021)].

Six months after randomisation (– 2 weeks/+ 4 weeks)

Assessments performed are detailed in the trial schedule of events (*Table 1*). The 6-month follow-up visit was scheduled to allow a minimum of 12 weeks' recovery from septoplasty surgery.

For participants allocated to the surgical arm, any complications from the septoplasty were recorded.

Twelve months after randomisation (± 2 weeks)

Assessments at the 12-month follow-up visit are detailed in the schedule of events (see *Table 1*).

TABLE 1 The NAIROS schedule of events

Procedures	Pre screening	Screening/consent/pre randomisation (visit 1)	Contact patient 2 weeks after randomisation (± 14 days)	Septoplasty [must occur any time up to 8 weeks (+ 4 weeks) after randomisation]	Contact patient 2 weeks after surgery (± 14 days)	6 months (− 2 weeks/ + 4 weeks) (visit 2)	12 months (± 2 weeks) (visit 3)
PIS given to patients referred to NAIROS clinic when appointment made	✓						
Eligibility assessment		✓ Pre randomisation					
Demographics (sex and age)		✓ Pre randomisation					
Medical history		✓ Pre randomisation					
Informed consent (must take place prior to any study-specific activities)		✓ Pre randomisation					
Eligibility confirmed		✓ Post consent and pre randomisation					
Clinical examination [includes nasal endoscopy (without decongestion) and baseline recording of four core features[a]]		✓ Post consent and pre randomisation				✓	✓
SNOT-22		✓ Post consent and pre randomisation				✓	✓
NOSE		✓ Post consent and pre randomisation				✓	✓
DOASS (post decongestion); only for patients consenting to the main trial		✓ Post consent and pre randomisation				✓	✓
Measurements of nasal patency (see *Report Supplementary Material 1* for further information) (only for patients consenting to the main trial)		✓ Post consent and pre randomisation				✓	✓
SF-36 (only for patients consenting to the main trial)		✓ Post consent and pre randomisation				✓	✓
HUQ						✓	✓
Randomisation (following complete assessments)		✓					

TABLE 1 The NAIROS schedule of events (*continued*)

Procedures	Pre screening	Screening/consent/pre randomisation (visit 1)	Contact patient 2 weeks after randomisation (± 14 days)	Septoplasty [must occur any time up to 8 weeks (+ 4 weeks) after randomisation]	Contact patient 2 weeks after surgery (± 14 days)	6 months (− 2 weeks/ + 4 weeks) (visit 2)	12 months (± 2 weeks) (visit 3)
Medical management arm: dispensing of trial drugs (only if randomised to medical management arm); 6-month supply of Stérimar isotonic spray and mometasone given		✓					
IMP and Stérimar usage (number of bottles used)						✓	
Septoplasty arm (must occur any time up to 8 weeks (+ 4 weeks[b]) after randomisation)				✓			
Post-surgery CRF				✓			
Feedback on patient well-being. Contact can be made via telephone, text or e-mail						✓	✓
Record technical failures from those operations in which widening of the nasal airway has been achieved, yet the patient's symptoms persist						✓	✓
If a participant did not attend the follow-up visit, telephone to remind them to complete/post SNOT-22[c]						✓	✓
Time and travel questionnaire							✓
AE assessments		✓	✓	✓	✓	✓	✓
Concomitant medications		✓	✓	✓	✓	✓	✓

CRF, case report form; IMP, investigational medicinal product.

a The four core features are (1) the side of the convexity, (2) the site of deflection (whether anterior or posterior or both), (3) endoscopy findings and (4) whether the extent of the airway block by the septum is < or > 50%.

b The additional 4-week window is to allow for extenuating circumstances only, such as unexpected patient or clinical reasons that necessitate a delay in surgery.

c SNOT-22 at 6 months and 12 months may be collected by post, e-mail or using the Castor electronic data capture online platform, whichever method is the most convenient for the patient if they are unable to make the clinic appointment.

Note

Reproduced from version 8.0 of the NAIROS protocol (17 December 2020) [see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/1422607#/ (accessed 30 July 2021)].

At both the 6- and 12-month visits, participants were given the option to discontinue allocated treatment and explore treatment options available within standard local NHS care.

Serious adverse event reporting

Adverse events were recorded from date of randomisation until the end of trial participation (at visit 3, 12 months post randomisation), at every trial visit and during the safety telephone calls described previously. AE severity was assessed by the investigator as mild/moderate/severe and assessed for causality and expectedness by reference to the Reference Safety Information. The Reference Safety Information for surgery (expected AEs) was documented in the protocol. The Reference Safety Information for the medical management arm intervention was section 4.8 of the approved summary of product characteristics for NASONEX® 50 µg/actuation (mometasone furoate) nasal spray (Merck Sharp & Dohme Corp., Rahway, NJ, USA). There were no known drug interactions listed in the approved summary of product characteristics.

Serious adverse events (SAEs) were reported to the NCTU and to the sponsor on a trial-specific report within 24 hours of the site becoming aware of the event and followed up until resolution. SAEs were reported until the end of the trial. All SAEs were summarised in the annual development safety update report to the MHRA and in the annual Clinical Trial of an Investigational Medicinal Product (CTIMP) safety report to the relevant REC.

Suspected unexpected serious adverse reactions (SUSARs) among participants in both arms underwent expedited reporting to the REC. Only SUSARs in the medical management arm required expedited reporting to the MHRA.

Definition of the end of the trial

The trial end was defined as the collection date of the final participant's 12-month follow-up data.

Patient and public involvement

Patient and public involvement was integrated into the design, conduct and outcome stages of the study. Substantial PPI input was sought in the design of the study. Initially, 21 patients were consulted shortly before undergoing septoplasty and asked about their symptoms, about their willingness to be randomised, and for feedback on the NOSE and SNOT-22. Two-thirds of patients preferred the SNOT-22, which better matched their symptoms (in particular, the NOSE omitted snoring and headache, which were felt to be important).

Of key concern to the patients were details of the treatment received in the medical arm and whether or not randomisation to this arm precluded them from future surgery. This first phase of PPI was used to design a trial outline, which was discussed with a further 18 outpatients with nasal obstruction. During the second phase of the PPI, we were able to adjust the time for which surgery would be deferred in the control arm, and the acceptability of the nature and timing of the outcome measures. Additional input was obtained during the development of patient experience.

On receipt of funding, a PPI panel was convened, with participants recruited via ENT clinics and VOICE (URL: www.voice-global.org). Recruitment materials for the panel outlined details of the study, the expected time commitment and reimbursement for time and expenses. A member of the panel presented a patient perspective on septoplasty and the NAIROS trial, at the NAIROS launch event. Two PPI meetings

with five panel members were held during study set-up to obtain input into the development of the recruitment strategy and other study processes (e.g. arrangements for participants who wished to discontinue their allocated treatment); feedback was also obtained on drafts of the PIS, consent form and recruitment video.

Subsequently, PPI panel input regarding specific patient-facing trial materials, including the trial website and the thank-you letter for trial participants, was obtained via e-mail on a more ad hoc basis. At each subsequent contact, before requesting any further input, a short update on trial progress was provided.

The Trial Steering Committee (TSC) included an independent PPI member. The TSC met regularly to review study documentation, including patient-facing documents and lay language text, and to ensure that the trial was conducted in a way that was considerate of the needs and wishes of participants.

Statistical considerations

The trial analysis followed a statistical analysis plan (SAP) (version 2.0, dated 25 March 2021). There was no formal interim analysis, only a single analysis after the database was locked on 29 January 2021. Decisions regarding the continuation of the trial were made at Data Monitoring Committee (DMC) meetings every 6 months.

Analyses are reported according to the Consolidated Standards of Reporting Trials (CONSORT) recommendations and were conducted in the validated statistical software package Stata®, version 16 (StataCorp LP, College Station, TX, USA).

Sample size calculation

The sample size calculation was based on a *t*-test for superiority assuming equal variance across groups, a conservative approach given the primary analysis was based on adjustment for the baseline values of SNOT-22, which generally increases statistical power. The target recruitment number of 378 participants allowed for a 20% drop-out rate (based on experience from two prior septal surgery audits).[86,87] The remaining 302 participants (151 per arm at completion) would be sufficient to deliver 90% power to detect a 9-point difference in the overall SNOT-22 score between arms. This assumed a 5% type I error rate and a standard deviation (SD) of 24 points. The MCID of 9 units was informed by relevant literature; it was felt to be the most relevant and a change of 8.9 units had been identified as being clinically meaningful.[43,45,46,88,89] The same literature was used to guide assumptions about what would be a reasonable value for the SD for the design parameter. We took a conservative approach as we assumed that the SD would be 24 points, which was the largest value reported.[43,45,46,88,89]

Statistical analysis plan

Primary outcome measure

The primary outcome measure was the SNOT-22 score at 6 months. SNOT-22 scores were recorded at baseline and at 6 and 12 months post randomisation. Baseline and follow-up data were summarised using appropriate statistics and graphical summaries. Box plots (e.g. *Figure 6*) show summary statistics of the measurement they represent. The box represents the middle 50% of the data (lower quartile to upper quartile), the line within the box shows the median (50th percentile), the whiskers show data that fall within 1.5 × the interquartile range (IQR) and the points show data that fall outside these limits. SNOT-22 questionnaires with up to 20% of items missing were imputed, with the average of the completed questions used for missing items.

Summary statistics of overall scores, including means with associated 95% confidence intervals (CIs), are presented by treatment group and overall in *Table 6*.

Defining the populations for analysis

The following analyses by population were undertaken:

- Intention-to-treat group – all ineligible and protocol-violator participants included in the analysis on an ITT basis, with participants kept in their randomised treatment group. This included outcome measures completed at any time.
- Compliant ITT group – all participants in the ITT group, but complying with questionnaires completed within the 6-month (– 2 weeks/+ 4 weeks) return window with no consideration given to septoplasty status.
- Per-protocol group – all participants who received the treatment they were randomised to and complied with protocol in terms of timings and compliance windows for the surgery and primary end point (6-month visit/SNOT-22 completion). This excluded participants randomised to septoplasty but who did not receive septoplasty within 12 weeks of randomisation, participants randomised to medical management who had actually received standard care septoplasty before the 6-month + 4-week primary end point, and participants whose primary end point was completed outside the compliance window.
- Per-treatment group – this was similar to the per-protocol group, with some additional participants included. The medical management group was exactly the same as in the per-protocol group. Any participant who was randomised to septoplasty and received their septoplasty at least 10 weeks before the primary end point was included in the septoplasty group. In addition, any participant randomised to medical management but who received septoplasty at least 10 weeks before the primary end point was completed was included in the septoplasty group.
- Non-randomised group – those eligible to be included in the NAIROS trial but who declined to take part. We planned to compare the non-randomised group with those consenting to take part in the trial; 45 patients agreed to join the non-randomised group and allow their data to be collected and analysed. However, owing to the small number of patients who agreed to join the non-randomised group (only 19 of whom provided NOSE data), a meaningful comparison between this group and those consenting to the trial could not be made and these data were not included in this report.

Analysis of the primary outcome

Primary analysis

The primary analysis was conducted by comparing scores of the two randomised treatment arms (immediate septoplasty and medical management) at 6 months. This analysis used multivariable linear regression.

The associated magnitude and significance of any between-arm differences were calculated in a multivariate regression model (referred to as model 1), adjusting for baseline severity SNOT-22 score as a continuous covariate and stratification factors at randomisation [(1) gender and (2) severity at baseline assessed by the NOSE].

Residual analysis was conducted to assess the goodness of fit of model 1. Model 1 is reported fully (see *Chapter 3*).

Sensitivity analyses

A number of sensitivity analyses of the primary analyses were conducted. The models for these analyses are outlined below:

- model 2 – adjusting for continuous baseline NOSE score, rather than the three categories used at baseline, to utilise the full information from the continuous measure
- model 3 – a series of multivariable analyses to further allow consideration of other important baseline factors in the regression model. This included age, ethnicity, site (as a random effect), smoking history, baseline levels of trial questionnaires (DOASS, endoscopy findings) and the four selected nasal patency variables.

Within the model 3 frame, non-linear relationships with continuous baseline covariates were explored for simple and suitable first order, and more complex fractional polynomial transformations, which were applied when appropriate. Building the optimal model for model 3 was based on a forward selection method (change in −2log likelihood, compared against a chi-squared distribution to assess variable inclusion). Variables were initially assessed using univariable regression against the primary outcome measure before they were included in the forward selection process; any variable with $p > 0.1$ was included in the forward selection process. The results of this first assessment, of all considered variables along with identified transforms, are presented in *Appendix 1*, *Table 48*. Significant variables at 5% level were retained in the final model ($p < 0.05$). At the end of the forward selection procedures, if any of the included covariates became non-significant ($p > 0.05$), the impact of removing them from the final model was assessed. Improved model suitability was assessed using Akaike information criterion, which estimates the quality of each model relative to the other models, thereby providing a means for model selection. The aim was to derive the most parsimonious model. The details of the full final model 3 can be found in *Appendix 1*, *Table 48*.

Secondary analyses

Secondary analyses of the primary outcome were performed by limiting the analysis to the specific populations: compliant ITT, per protocol and per treatment. Multiple imputation was used to include all patients who consented and were randomised, including those with missing SNOT-22 scores at the primary end point. Missing data were imputed using multiple imputation with the proportion of missing data in each group reported and compared descriptively (see *Report Supplementary Material 6*). Descriptive statistics of baseline variables are presented by treatment group and missing data status (with and without primary end point data, i.e. SNOT-22 score at 6 months). Baseline variables found to be predictive of missing data status are included in multiple imputation equations.

We used multiple imputation to minimise bias, to maximise use of available information and to obtain appropriate estimates of uncertainty. One thousand multiple imputation data sets were created in Stata 16 using chained equations. The multiple imputation equation includes baseline data on gender; NOSE categories and baseline SNOT-22 score; and predictors of missing data to make the missing-at-random assumption as plausible as possible. A conservative approach was adopted, and treatment group was included in the imputation model.

Secondary outcome measures

The analysis of secondary outcomes followed a broadly similar strategy to the primary outcome measure. Secondary outcomes included data at the 6-month follow-up from the other outcomes [i.e. NOSE, DOASS, PNIF (maximum of three measurements), NPR from MIV (using mean volumes from three measurements) and tidal breathing] and data for all outcomes at the 12-month follow-up. SNOT-22 subscales (rhinologic, sleep, ear/facial pain, psychological) at the three time points are presented.

Summary statistics and graphical representation of subjective scales were tabulated at randomisation and at 6 and 12 months' follow-up, both by intervention arm and collectively. Multiple regression was used to compare the outcome scores between treatment groups at follow-up time points. Variation between sites was included as a random effect with an assumed normal distribution, with analysis including the stratification factors of baseline severity and gender. Further adjusted analyses included terms for baseline values of the scores and key demographic and clinical covariates.

Adverse events were tabulated according to the World Health Organization Common Terminology Criteria for Adverse Events, version 4.03, with the number of severe AEs (Common Terminology Criteria for Adverse Events grade 3, 4 or 5) reported as a proportion of all AEs. The number of participants experiencing at least one severe AE according to the Common Terminology Criteria for Adverse Events was reported as a proportion of all participants. Surgical complication/failure and reintervention were described and not subjected to statistical testing. Technical failures (defined as occasions when the participant self-reported symptoms remaining the same or worsening, along with surgeon opinion on

whether revision surgery was required) from operations in which widening of the nasal airway was achieved were reported. Complications experienced as a result of the septoplasties are also presented in the results chapter.

We carried out a subgroup analysis for participants who were recommended to receive the inferior turbinate reduction. This led to four groups: as randomised, recommended for turbinate reduction or not. This broadly followed the primary analysis, but analysis was carried out separately for each subgroup. Subgroups by gender are also reported.

Subpopulation analyses

The subpopulation treatment effect pattern plot (STEPP) analysis[90–93] approach was developed to allow researchers to investigate the heterogeneity of treatment effects on outcomes across values of a (continuously measured) covariate. STEPP is a graphical tool which allows one to visualise treatment differences, and will be useful for guiding patients and clinicians when making decisions regarding treatment choice.

The importance of baseline severity as a continuous distribution of NOSE score at randomisation was further explored graphically by STEPP analysis to display the predicted point estimates of any treatment effect (with 95% CIs) over the range of NOSE values (which ranged from 30–100 among NAIROS participants), with the aim of further informing any patient selection guidance and recommendations. The STEPP analysis was also carried out for overlapping ranges of NOSE score separately by gender.

Data monitoring, quality control and assurance

The NCTU was delegated by the sponsor to monitor trial conduct and data integrity to ensure that the trial was conducted in accordance with the protocol and the latest directive on good clinical practice (2005/28/EC).[94] All final statistical and health economics analyses were reviewed for quality assurance by independent researchers.

Trial management and oversight

The sponsor delegated day-to-day management of the trial to the NCTU and the TMG, which met approximately monthly. External, independent oversight of the trial was provided by an independent DMC and a TSC who reviewed the SAP. Details of these committees and trial monitoring have previously been described in the published protocol paper.[80] Terms of reference and trial oversight charters described roles and responsibilities of individual committees. Members were required to sign the relevant terms of reference or trial oversight charter, declaring any conflict of interest. The TSC met at least annually after the DMC meeting.

Chapter 3 Results

The analysis presented here is reported according to the CONSORT flow diagram (see *Figure 3*) and is based on the SAP version 2.0 (25 March 2021). SAP version 1.0 (1 February 2021) was approved immediately before data download. A further minor clarification on the definitions of 'per-protocol' and 'per-treated' analyses populations was required in the SAP following data download; hence, version 2.0 was used for the analysis. The SAP provided guidelines for the analysis of the NAIROS trial data. Any analyses that were not prespecified in the SAP are denoted as 'unplanned'.

Recruitment

- Number of sites: 17.
- Date first site opened: 18 January 2018.
- Date first participant randomised: 26 January 2018.
- Total number of participants randomised: 378.
- Date last participant recruited (consented): 5 December 2019.
- Date last participant randomised: 5 December 2019.
- Date of last participant follow-up: 17 December 2020.
- Date of final data set download: 3 February 2021.

Randomisation and stratification factors

The trial recruited to target. Individual randomisation to the two trial arms was stratified by gender and NOSE category (see *Chapter 2*). The numbers of participants randomised by strata are presented in *Table 2*.

Two-thirds of randomised participants were males. The relative frequencies of NOSE severity levels were 16% for moderate, 47% for severe and 37% for extreme.

Treatment allocation by stratification factors for the ITT population is presented in *Appendix 1*, *Table 25*.

Site recruitment activity is presented in *Appendix 1*, *Table 26*.

TABLE 2 Participant treatment allocation by stratification factors

	Trial arm, *n* (%)		
Stratification factor	**Septoplasty (*N* = 188)**	**Medical management (*N* = 190)**	**Total (*N* = 378), *n* (%)**
Moderate/male	21 (11)	22 (12)	43 (11)
Moderate/female	9 (5)	10 (5)	19 (5)
Severe/male	60 (32)	61 (32)	121 (32)
Severe/female	29 (15)	28 (15)	57 (15)
Extreme/male	45 (24)	44 (23)	89 (24)
Extreme/female	24 (13)	25 (13)	49 (13)
Total	188 (100)	190 (100)	378 (100)

Participant flow: Consolidated Standards of Reporting Trials flow diagram

Recruitment and participant flow through the trial is reported in the CONSORT diagram (*Figure 3*).

Appendix 1, *Table 27*, summarises weeks from randomisation to withdrawal from trial. *Appendix 1*, *Table 28*, presents a line listing of reasons for withdrawing.

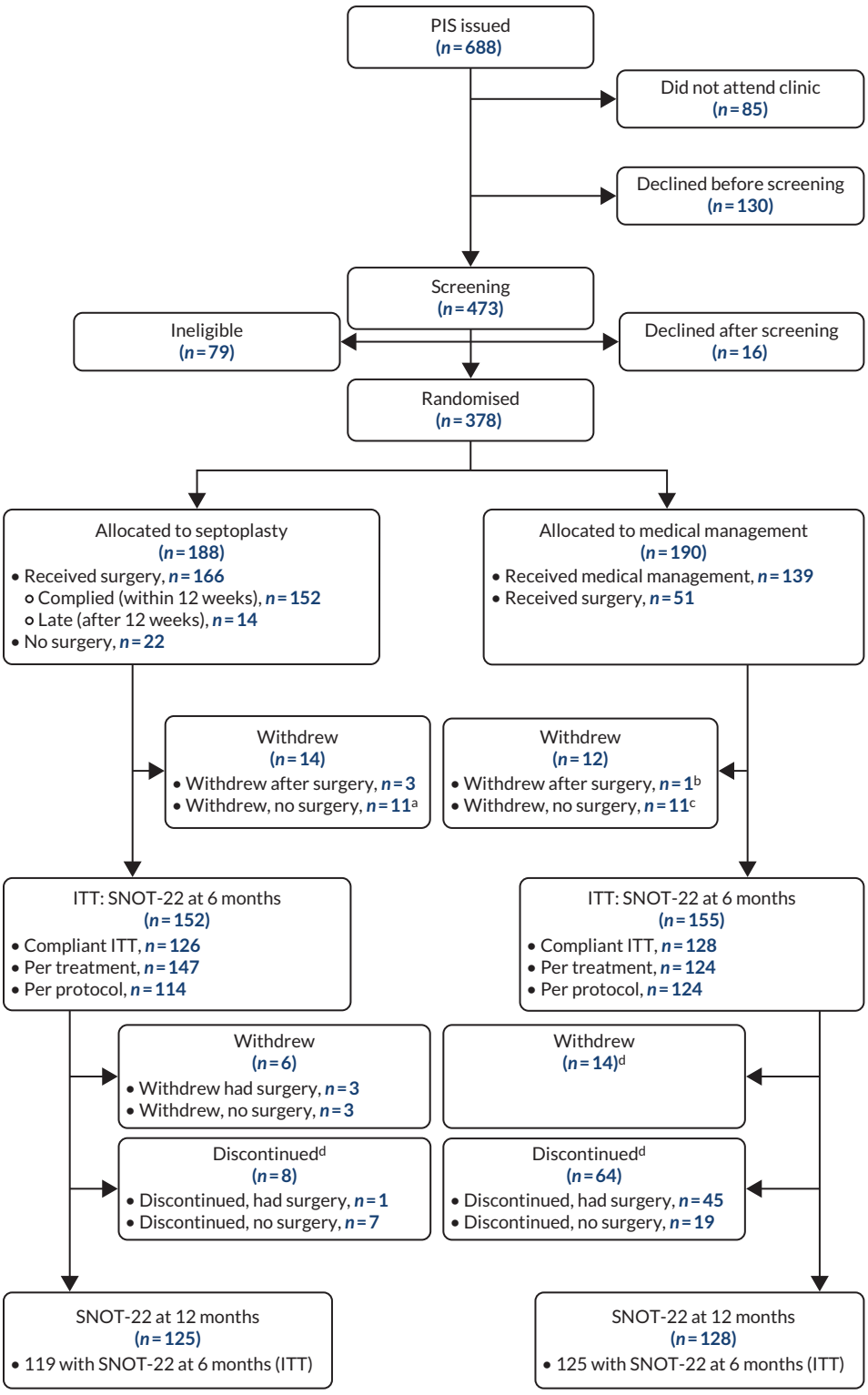

FIGURE 3 The CONSORT flow diagram. a, Discontinued, no surgery (n = 8); b, discontinued, had surgery (n = 1); c, discontinued, no surgery (n = 1); d, discontinued, had surgery (n = 5).

As can be seen from the CONSORT diagram (see *Figure 3*), 16 participants randomised to septoplasty and 71 participants randomised to medical management discontinued their allocated treatment. Details of the reasons for treatment discontinuation can be found in *Appendix 1*, *Tables 29* and *30* (septoplasty arm) and *Tables 31* and *32* (medical management arm). The most common reasons given by medical management participants for discontinuing were 'not happy with the sprays'/'side effects of sprays' [reported by 76 out of 98 (78%) participants] and worsening symptoms [reported by 15 out of 98 (15%) participants].

Baseline demographic data

Demographic and baseline characteristics (*Table 3*) show that, overall, 67% of participants were male, 88% were white and the average participant age was 39.8 years.

Summary tables of baseline medical history (see *Table 33*), clinical examination (see *Table 34*), and endoscopy findings (see *Table 35*) are presented in *Appendix 1*. *Appendix 1*, *Table 36*, shows the range of timings for decongestant in relation to when the nasal patency measurements were taken (there are validity requirements for 'post-decongestant measurement start time' to be at least 5 minutes after 'time decongestant spray given', and for 'post-decongestant measurement end time' to be within 60 minutes of 'time decongestant spray given').

TABLE 3 Participant demographics and continuous NOSE score at baseline, by arm and overall

Demographic and NOSE score	Trial arm		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Total (*N* = 378)
Gender, n (%)			
Male	126 (67)	127 (67)	253 (67)
Female	62 (33)	63 (33)	125 (33)
Age (years)			
Median (IQR)	38 (27.5–51)	37 (28–50)	38 (28–50)
Mean (SD)	40.3 (14.9)	39.4 (13.9)	39.8 (14.4)
Minimum, maximum	18, 79	18, 80	18, 80
Ethnic group, n (%)			
White	169 (90)	165 (87)	334 (88)
Asian (Indian/Pakistani/Bangladeshi ancestry)	13 (7)	14 (7)	27 (7)
Other Asian	1 (< 1)	2 (1)	3 (< 1)
Other ethnic origin	3 (2)	9 (5)	12 (3)
Missing	2 (1)	0 (0)	2 (< 1)
Baseline NOSE score (continuous)			
Median (IQR)	70 (60–82.5)	70 (60–85)	70 (60–85)
Mean (SD)	69.9 (17.4)	71.3 (17.3)	70.6 (17.4)
Minimum, maximum	30, 100	30, 100	30, 100

Outcome data quality and completeness

A small number of returned questionnaires were only partially completed. Four SNOT-22 questionnaires had missing items at baseline, five had missing items at the primary end point of 6 months and four had missing items at the final 12-month data collection point. All of these were imputed by using the mean of the completed items as each had < 20% missing. One participant had one item missing from their NOSE questionnaire (20%) at the 6-month follow-up visit. This was also imputed using the mean of the other four responses.

Appendix 1, *Table 37*, shows data completeness in terms of the number of questionnaires returned at baseline and at the 6- and 12-month follow-up time points for the analysis groups, with an indication of numbers with partial or completely missing questionnaires.

Trial analysis populations

The full details of the populations used for the statistical analysis are defined in *Chapter 2*.

Table 4 displays analysis populations, based on compliance with the allocated intervention and the primary end point.

The primary analysis for this trial is on the ITT population with the primary outcome, SNOT-22, collected at the 6-month follow-up visit. The randomised participants who completed the SNOT-22 at 6 months [*n* = 307 (81%)] (see *Table 4*) comprise the ITT population.

Compliance, treatment received and numbers analysed

Appendix 1, *Table 38*, shows when the SNOT-22 questionnaires were completed in relation to the visit window of −2/+4 weeks stated in the protocol. Compliance with SNOT-22 completion is balanced between the two arms, with 83% of the ITT population complying with the primary end point visit window at 6 months, and 66% of those attending the 12-month visit completing the SNOT-22 questionnaires within the compliance window. *Table 4* summarises key features of participants' trial pathways and provides numbers for each of the specified analysis populations.

Consultant surgeons carried out 128 out of the 166 (77%) septoplasties undertaken among participants randomised to the septoplasty arm. Seventeen (10%) septoplasties were carried out by associate specialists and 16 (10%) septoplasties were carried out by surgeons of other grades. The records of five (3%) participants did not include the grade of the most senior operative surgeon. Further operative details can be found in *Appendix 1*, *Tables 39* and *40*.

The average septoplasty duration was 56 minutes. Data were available for 159 of the 166 septoplasty participants. Summary statistics are presented in *Appendix 1*, *Table 41*.

Details of participant compliance with the medication of the medical management arm (nasal spray usage) are provided in *Appendix 1*, *Tables 42* and *43*. When asked 'Over the last month have you used the NAIROS medication (nasal steroid and/or saline sprays)?', 122 (64%) participants confirmed that they had. The quantities of bottles used are also presented in *Appendix 1*, *Tables 42* and *43*. Sixty-nine (36%) participants provided this information for saline and 65 (34%) participants provided this information for steroids. The median number of saline spray bottles used was 3.5 (IQR 2.5–5) (*n* = 69). The median number of steroid spray bottles used was 4 (IQR 3–5.5) (*n* = 65). The reasons for participants ceasing use of the sprays are summarised in *Appendix 1*, *Tables 42–44*.

TABLE 4 Protocol compliance in relation to allocated treatment and the primary end point

Randomised arm	Complied with allocated intervention[a]	Primary end point status[b]	Protocol compliance	Number of participants (*N* = 378)	Withdrew (*n*)	ITT (*n*)	Compliant ITT (*n*)	Per protocol (*n*)	Per treatment (*n*)
Septoplasty	Complied	Complied	Complied	114	1	114	114	114	114
Septoplasty	Complied	Did not comply	Did not comply	23	2	23	0	0	23
Septoplasty	Complied	No primary end point received	Did not comply	15	3	0	0	0	0
Septoplasty	Did not comply	Complied	Did not comply	8	0	8	8	0	8
Septoplasty	Did not comply	Did not comply	Did not comply	3	0	3	0	0	0
Septoplasty	Did not comply	No primary end point received	Did not comply	3	0	0	0	0	0
Septoplasty	No surgery	Complied	Did not comply	4	1	4	4	0	0
Septoplasty	No surgery	No primary end point received	Did not comply	18	13	0	0	0	0
Total septoplasty				188	20	152	126	114	145
Medical management	Complied	Complied	Complied	89	3	89	89	89	89
Medical management	Complied	Did not comply	Did not comply	19	3	19	0	0	0
Medical management	Complied	No primary end point received	Did not comply	31	14	0	0	0	0
Medical management	Did not comply (received surgery)	Complied	Did not comply	39	4	39	39	35	35 + 2[c]
Medical management	Did not comply (received surgery)	Did not comply	Did not comply	8	1	8	0	0	0
Medical management	Did not comply (received surgery)	No primary end point received	Did not comply	4	1	0	0	0	0
Total medical management				190	26	155	128	124	124 + 2*
Trial total				378	46	307	254	238	271

a Compliance measured by receiving the allocated intervention within the time frame specified in the protocol.
b Compliance measured by completing the SNOT-22 within the 6 months – 2/+ 4 weeks' window.
c Included in septoplasty per-treatment group.

Note
Shading indicates participants who did not receive their allocated treatment (septoplasty, *n* = 22; medical management, *n* = 51).

Time from randomisation to septoplasty

Figure 4 displays time to surgery for participants randomised to the septoplasty arm and for whom primary end point data were collected (ITT population). The red solid line shows the 8-week compliance window for septoplasty. The red hatched line shows the additional 4-week window that allowed for delays in delivering septoplasty in extenuating circumstances.

Most participants [166 out of 188 (88%)] randomised to septoplasty did receive the operation (see *Table 4*). Of these 166 participants, 148 (89%) were included in the ITT population, meaning that they had primary outcome data collected. Of these 148 participants in the ITT population, 137 (93%) received septoplasty within the compliance window.

Figure 5 shows the distribution of time elapsed from point of randomisation to septoplasty carried out for the ITT population originally randomised to the medical management arm who discontinued treatment and opted to receive non-trial septoplasty.

Six NHS septoplasties for participants discontinuing the medical management treatment were carried out beyond the end of the trial follow-up period (12-month visit + 2 weeks). For all presented analyses, these participants were classified as not receiving septoplasty.

Descriptive analysis of the primary outcome measure, the Sino-nasal Outcome Test-22 items

The SNOT-22 was measured at baseline and at 6 and 12 months. The distribution of scores at baseline by randomised arm can be seen in *Appendix 1*, *Figure 23*.

The SNOT-22 scores at baseline and at the primary end point (6-month visit) by allocated treatment group, and overall using descriptive statistics, are summarised in *Table 5*. Parametric and non-parametric variables are given as the score is integer in nature, but was treated as a continuous measure.

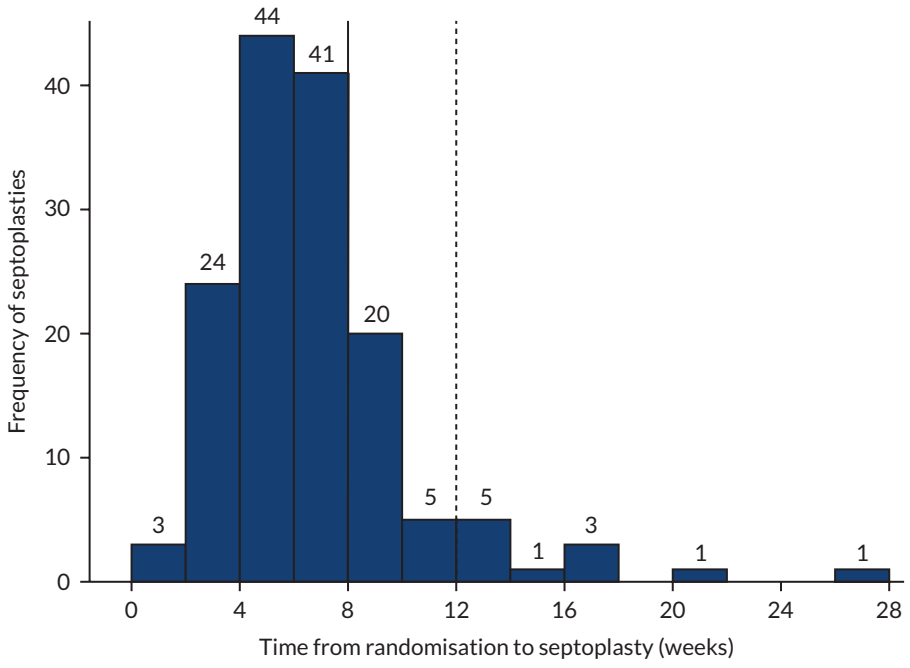

FIGURE 4 Distribution of time from randomisation to septoplasty.

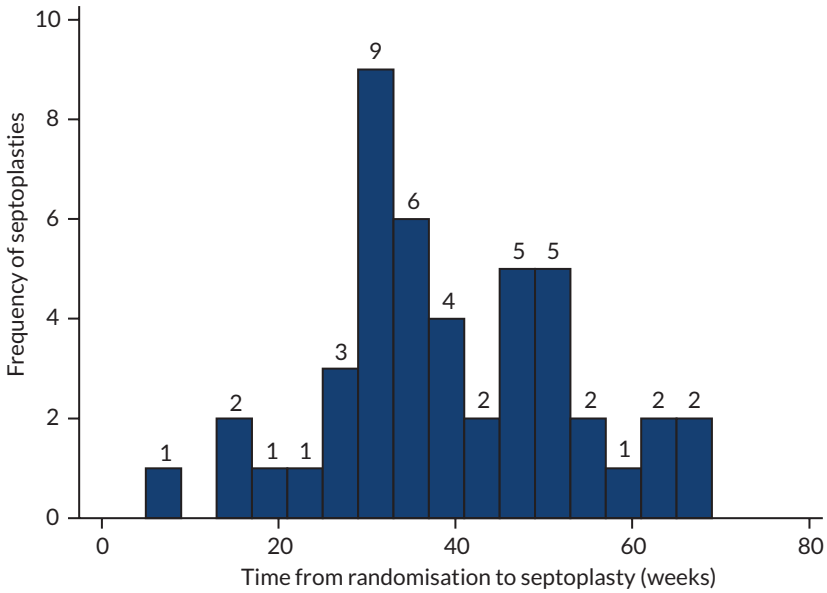

FIGURE 5 Distribution of time from randomisation to surgery for the ITT population participants randomised to the medical management arm who discontinued treatment and opted to receive non-trial septoplasty [*n* = 46 (24%)].

As expected, no major differences are observed at baseline across both arms of randomised participants in the ITT population. *Table 5* shows that the ITT groups in both arms have similar scores at baseline. The SNOT-22 scores at the 6-month follow-up visit are also presented in *Table 5*. The raw data alone show a large difference between the arms, specifically much lower scores (i.e. an improvement in symptoms) in the septoplasty arm. The raw data for the SNOT-22 scores at all three study visits are shown in *Figure 6*. At 12 months, 253 (67%) participants provided SNOT-22 outcome data; 244 of these were included in the ITT group (i.e. also completed the SNOT-22 at 6 months).

Appendix 1, *Table 45*, shows the summary statistics for the SNOT-22 score at 12 months (secondary outcome).

The SNOT-22 scores as raw data in box plots for the ITT population (i.e. those with primary outcome data) and those with outcome data at 12 months are shown in *Figure 6*. It is interesting that scores tend to reduce (improve) over time in the medical management arm, but symptomatic improvement is more marked in the septoplasty arm. The improvement in scores is evident at 6 months and seems to be maintained at 12 months. Some of the improvement at 12 months in the medical management arm may have been influenced by the 37 participants who were randomised to medical management but received non-trial septoplasty after 6 months. The SNOT-22 scores for this subset of 37 participants are displayed alongside those who did not discontinue allocated treatment in *Figure 7*.

The participants in the medical management who did not receive non-trial septoplasty still show further improvement in symptoms at 12 months, but for the most part, this is clearly a smaller improvement than is shown in the 37 participants who received non-trial septoplasty in the second half of the trial. Those who requested septoplasty did not exhibit improvement in their 6-month SNOT-22 scores in comparison with baseline, despite the prescribed medical management. *Figure 7* omits five participants who received their septoplasty before the 6-month follow-up visit (primary end point).

Appendix 1, *Table 46* shows the timing of septoplasties, in relation to the primary end point, carried out on participants randomised to medical management who had non-trial septoplasty.

TABLE 5 The SNOT-22 summary statistics at baseline and at the primary end point (6 months) by arm and overall (all participants and ITT population)

	SNOT-22 scores								
	Septoplasty (*N* = 188)			Medical management (*N* = 190)			Overall (*N* = 378)		
ITT population	All, baseline	ITT, baseline	ITT, 6 months	All, baseline	ITT, baseline	ITT, 6 months	All, baseline	ITT, baseline	ITT, 6 months
Population, *n* (%)	188 (100)	152 (81)	152 (81)	190 (100)	155 (82)	155 (82)	378 (100)	307 (81)	307 (81)
Median (IQR)	44 (26.5–56.5)	44 (26.5–57)	15 (6–27)	41.5 (27–61)	42 (27–63)	38 (22–54)	42.5 (27–59)	43 (27–59)	25 (11–45)
Mean (SD)	44.0 (20.4)	44.5 (20.8)	19.9 (18.0)	44.0 (21.5)	44.1 (21.1)	39.5 (21.4)	44.0 (21.0)	44.3 (20.9)	29.8 (22.1)
95% CI about mean	41.1 to 47.0	41.1 to 47.8	17.0 to 22.7	40.9 to 47.1	40.8 to 47.4	36.1 to 42.9	41.9 to 46.1	41.9 to 46.6	27.3 to 32.3
Minimum, maximum	6, 104	6, 104	0, 78	6, 96	6, 92	5, 85	6, 104	6, 104	0, 85

Note
The range of scores is 0 to 110, with higher scores representing worse symptoms.

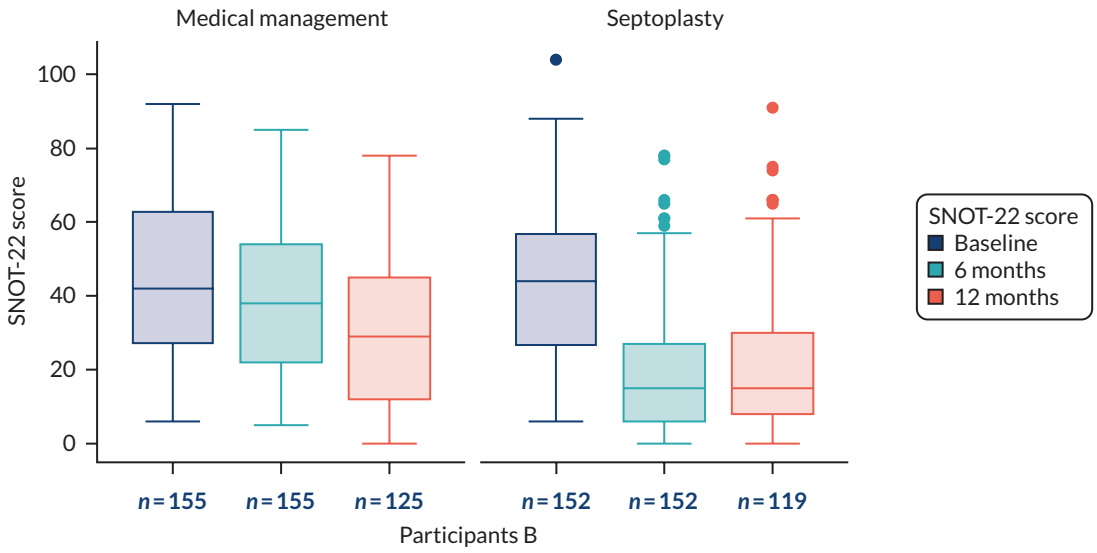

FIGURE 6 The SNOT-22 scores at each study visit (baseline, 6 months and 12 months).

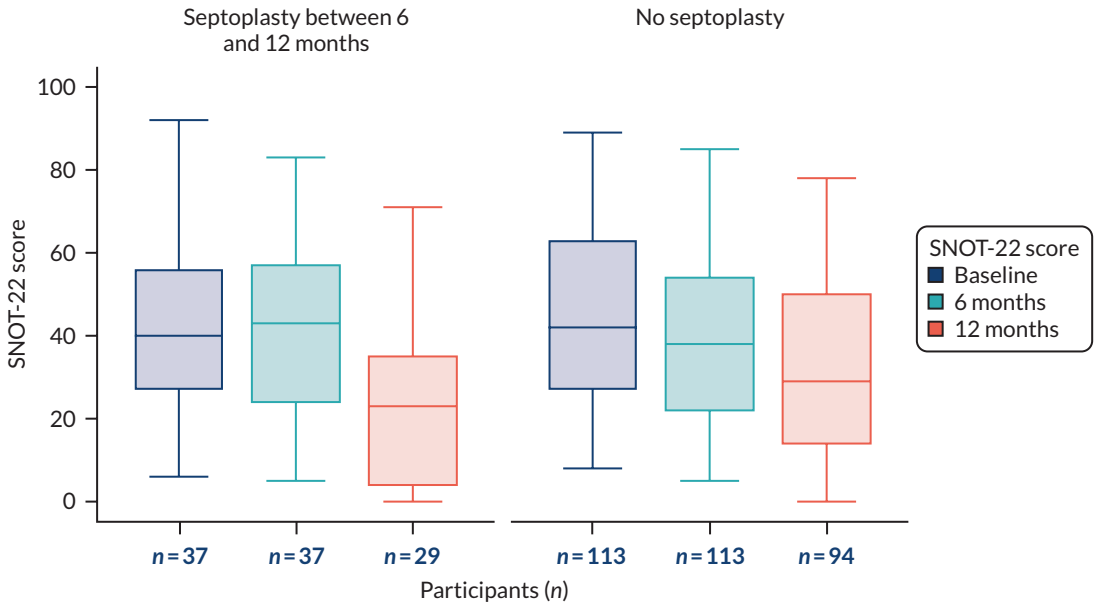

FIGURE 7 The SNOT-22 scores in the medical management arm, differentiated by whether or not participants had non-trial septoplasty after 6 months (ITT population). On the left, those participants who elected to have non-trial septoplasty between 6 and 12 months. On the right, those participants who did not have non-trial septoplasty.

Efficacy analysis: primary outcome

We performed the ITT analysis on the 307 participants for whom we had SNOT-22 data at 6 months. This is the primary analysis (model 1) of the primary outcome measure of this trial, as specified in the protocol.

Model 1: the primary outcome measure is the SNOT-22 score assessed at 6 months. We analysed this score using multivariable regression models; this analysis enabled us to compare this score between the treatment groups. The associated significance of any observed difference is calculated, adjusting any treatment effect by baseline SNOT-22 score and stratification factors at randomisation [(1) gender and (2) severity at baseline (according to three NOSE categories reported in the literature[95])]. The full specification of the fitted model is shown in *Table 6*. With the presence of baseline SNOT-22 score in

TABLE 6 Primary analysis model 1 summary: SNOT-22 score at 6 months (primary end point) adjusted for baseline SNOT-22 score and stratification factors (ITT population)

	Primary outcome measure: SNOT-22 score at 6 months				
Model 1	**Coefficient**	**SE of coefficient**	**Test statistic**	***p*-value**	**95% CI coefficient**
Arm: septoplasty (reference category: medical management)	−20.013	1.836	−10.90	< 0.0001	−23.625 to −16.40
Baseline SNOT-22 score	0.497	0.053	9.39	< 0.0001	0.393 to 0.601
Gender: male (reference category: female)	−0.553	1.944	−0.28	0.776	−4.379 to 3.272
NOSE severity: severe (reference category: moderate)	1.981	2.961	0.67	0.504	−3.846 to 7.808
NOSE severity: extreme (reference category: moderate)	5.811	3.459	1.68	0.094	−0.995 to 12.617
Constant	14.954	3.291	4.54	< 0.0001	8.479 to 21.430

SE, standard error.

Note
n = 307, adjusted R^2 = 0.4719, probability ≥ F ≤ 0.0001.

the model, the stratification variables do not appear to have a major influence on the primary outcome. However, there is a suggestion that those with extreme NOSE scores at baseline will tend to have scores, on average, 5.8 units higher than those with moderate scores at baseline.

Baseline SNOT-22 scores (see *Table 5*) are highly predictive of scores at outcome. On average, scores at 6 months tend to be 50% of the baseline score (this trend is suggested in *Figure 9* for the medical management arm). Most importantly, model 1 (see *Table 6*) shows a statistically significant effect for randomisation to the septoplasty arm, with scores, on average, being 20 units lower (adjusted difference −20.01, 95% CI −23.63 to −16.40; p < 0.0001) than those in the medical management arm (while ensuring all other variables are the same). The lower limit of the 95% CI is −16.40 units, well below the −9 MCID units assumed for the superiority margin.

Goodness of fit for model 1 was assessed by a series of plots of residuals. The residuals appeared normally distributed with no apparent pattern in fitted values versus residuals; fewer of the standardised residuals fell outside the range (−2 to 2) (see *Appendix 1*, *Figure 24*).

Sensitivity analyses

Four sensitivity analyses for the ITT population were planned, as detailed in *Chapter 2*. The results are summarised in *Figure 8*, in which the unplanned mixed-effect model demonstrates little impact of site as a random effect. The MCID of −9 units is indicated by the vertical hatched line in *Figures 8* and *9*. Details of the variable transformation and selection for model 3 can be found in *Appendix 1*, *Tables 47* and *48*. *Figure 8* shows that very little difference to the strength or magnitude of the signal is seen when considering the sensitivity analyses and including multiple imputation to address missing primary outcome data. Multiple imputation was used to include the full set of participants who consented and were randomised, including those with missing SNOT-22 scores at the primary end point. The proportion of missing data in each group is reported and compared descriptively. Descriptive statistics of baseline variables are presented by treatment group and missing data status (with and without primary end point data, i.e. SNOT-22 score at 6 months). All baseline variables were assessed, but none was found to be predictive of missing data status; therefore, they were not included in multiple imputation equations (see *Report Supplementary Material 6*). The multiple imputation model included the stratification variables that were recorded, and none was missing.

FIGURE 8 Results of the sensitivity analyses for the ITT population (model 1) and models 2, 3 and 3a, and including multiple imputation.

Figure 9 shows the secondary analysis of the primary outcome by the three distinct analysis populations (compliant ITT, per protocol and per treatment). These results are very similar to those of the primary analysis. There is a slight reduction in the magnitude of the effect in the compliant ITT analysis to around 18 units, but the 95% CI limits are still well beyond the MCID of −9 units.

Overall summary following primary analysis and sensitivity analyses

- Marked improvement seen in the septoplasty arm, with an average difference of −20 units (95% CI −24 to −16; $p < 0.0001$), compared with the medical management arm, at 6 months.
- The lower limit of the 95% CI for SNOT-22 score improvement is −16.40 units, which is substantially greater in magnitude than the MCID of −9 units used in the sample size justification for the trial.
- All sensitivity and secondary analyses show very similar results. There is strong pragmatic evidence that septoplasty is effective at reducing SNOT-22 score at 6 months, compared with medical management.

Descriptive analysis of secondary outcomes

This section covers the DOASS, the NOSE, rhinospirometry measurements, SNOT-22 scores at 12 months and SNOT-22 subscales. For each outcome measure, descriptive data and, when appropriate, the analysis comparing septoplasty with medical management for the available ITT population are presented.

Double Ordinal Airway Subjective Scale

The DOASS is a PROM; it collects data (a score) for each nostril. *Appendix 1*, *Figure 25*, shows the raw data collected from randomised participants at each time point, by nostril (better and worse). The summary statistics of the raw data are tabulated in *Appendix 1*, *Table 53*.

The raw data are presented in terms of worse and better nostrils. These data are paired (both nostrils measured) at each time point. The nostril with the lower score at baseline is defined as worse, and the nostril with the higher score is defined as better (range 1–10). The nostrils defined as worse and better at baseline are presented at the 6- and 12-month follow-up time points. We used the scores taken at the 6-month follow-up to define which nostril was better or worse for participants whose nostrils both had the same score at baseline.

Appendix 1, *Figure 25* shows that, for participants randomised to septoplasty, the score for the worse nostril had improved by the 6-month follow-up. The difference in scores between the worse and better nostrils reduced dramatically among septoplasty patients at 6 months. The differences between the worse and better nostrils are less evident in the medical management group follow-up scores, although improvement over time is seen in both groups.

Subjective Double Ordinal Airway Subjective Scale

One method to present the DOASS as a single summary ratio is the subjective DOASS. This representation of the magnitude of the differences between the two sides is generally presented as the NPR, calculated as (left score − right score) ÷ (left score + right score). Using the subjective DOASS was advisable as this same formula is also used to combine rhinospirometry paired nostril data. As we consider that laterality is irrelevant, we present absolute subjective DOASS, which is the modulus of the subjective score (i.e. sign is ignored). Scores close to zero mean that there is little difference between the nostrils. Summary statistics for absolute subjective DOASS NPR can be found in *Appendix 1*, *Table 50*.

Figure 10 shows that scores tend to be closer to zero (symmetrical nasal passages) for the septoplasty arm, which shows a reduction in subjective severity at 6 months. There is evidence of a more modest improvement in the medical management arm at 12 months.

FIGURE 9 Secondary analysis of the primary outcome by the three analysis populations (compliant ITT, per protocol and per treatment).

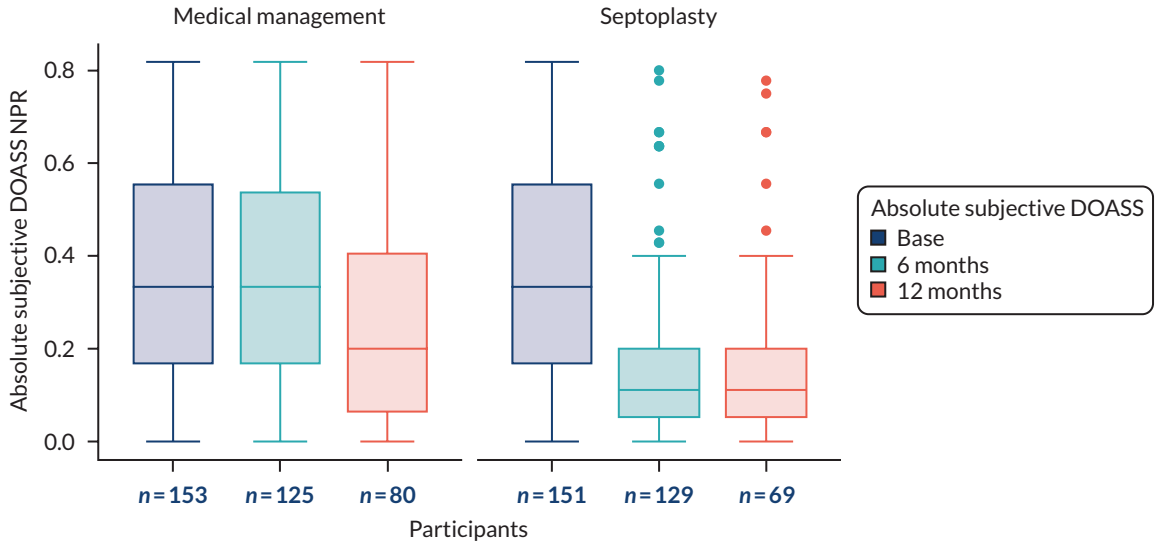

FIGURE 10 Absolute subjective DOASS.

Sino-nasal Outcome Test-22 items subscales

Summary statistics for the SNOT-22 subscales at all three study visits are presented in *Appendix 1*, *Table 51*. The corresponding box plots are shown in *Figure 11*.

The sleep and nasal subscales comprise 8 of the 22 items in the questionnaire; the otological subscale comprises four items and the emotional subscale comprises the remaining two items.

Appendix 1, *Table 51*, and the associated box plots (see *Figure 11*) show that improved and maintained scores in the septoplasty arm, and modest improvement in the medical management arm, are found in all subscales at both 6 and 12 months. The subscale scores range from 0–40 (sleep and nasal subscales), 0–20 (otologic subscale) and 0–10 (emotional subscale).

Nasal Obstruction Symptom Evaluation

The PROM NOSE scores were collected at baseline and used as a randomisation stratification variable. NOSE scores were also collected at 6 and 12 months. Continuous NOSE scores at baseline are summarised in *Table 7* by allocated treatment group and overall using descriptive statistics.

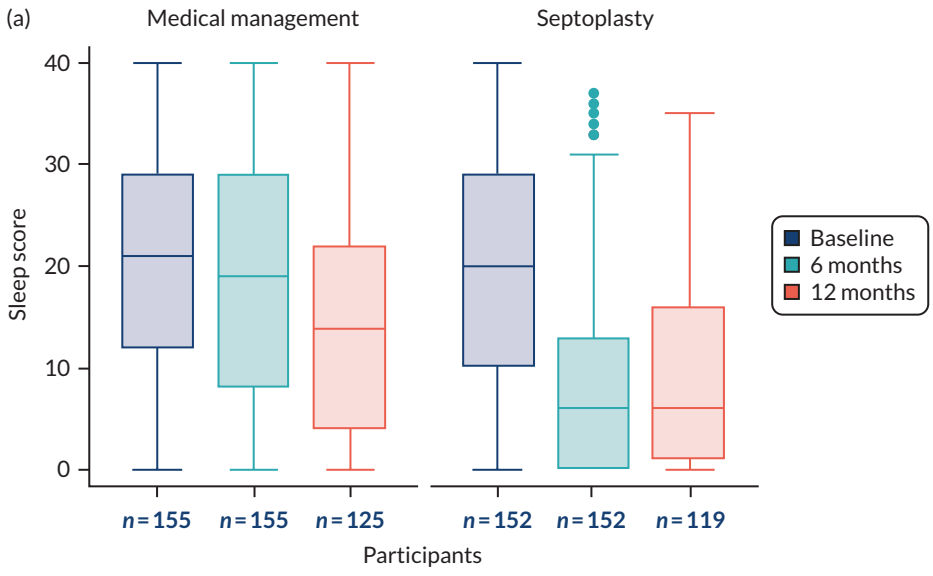

FIGURE 11 The SNOT-22 subscales. (a) Sleep score; (b) nasal score; (c) otologic score; and (d) emotional score. (*continued*)

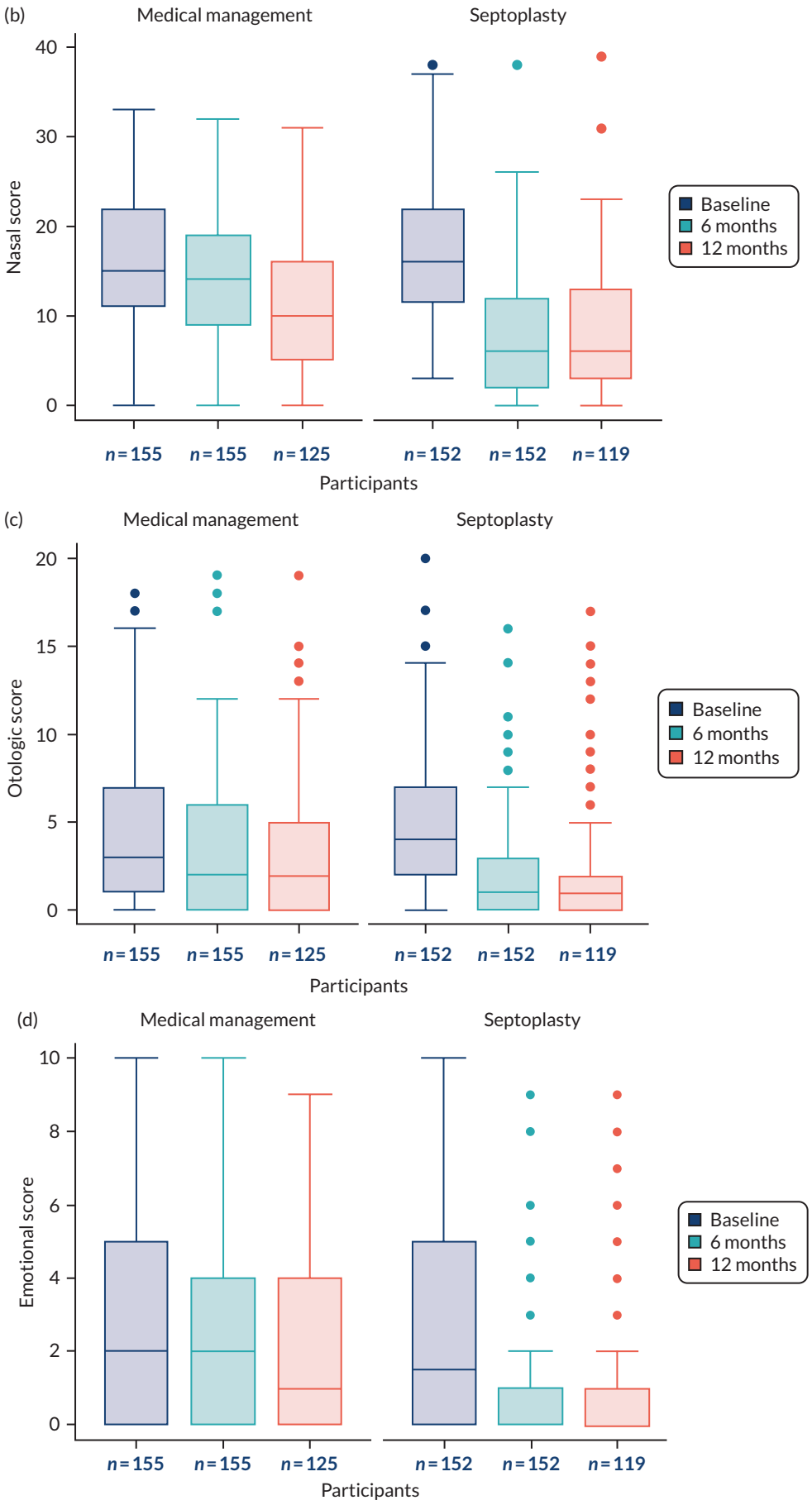

FIGURE 11 The SNOT-22 subscales. (a) Sleep score; (b) nasal score; (c) otologic score; and (d) emotional score.

TABLE 7 The NOSE scores at baseline, 6 months (primary end point) and 12 months, ITT population

	Baseline			6 months			12 months		
NOSE score ITT population summary statistics	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
ITT population, *n* (%)	152 (81)	155 (82)	307 (81)	145 (77)	144 (76)	289 (76)	105 (56)	118 (62)	223 (59)
Median (IQR)	70 (60–82.5)	70 (60–85)	70 (60–85)	20 (10–45)	62.5 (50–80)	45 (20–70)	25 (10–50)	50 (20–70)	35 (15–60)
Mean (SD)	70.8 (16.6)	71.7 (16.9)	71.3 (16.7)	29.0 (24.8)	62.2 (23.9)	45.5 (29.4)	30.7 (25.9)	47.3 (29.8)	39.5 (29.2)
95% CI about mean	68.1 to 73 to 4	69.0 to 74.4	69.4 to 73.1	24.9 to 33.1	58.3 to 66.2	42.1 to 49.0	25.7 to 35.7	41.8 to 52.7	35.6 to 43.3
Minimum, maximum	30, 100	30, 100	30, 100	0, 100	5, 100	0, 100	0, 100	0, 100	0, 100

As demonstrated by the overlapping CIs (and as expected for a randomised trial) there is no evidence of a difference in baseline scores between the two arms.

However, as evidenced by non-overlapping CIs, there are significant differences at the 6-month (primary end point) and 12-month follow-ups.

The NOSE score can range from 0 to 100, with higher scores representing worse symptoms. NOSE scores are similar at baseline across both treatment groups, as would be expected with random allocation (see *Appendix 1*, *Figure 26*). *Figure 12* shows that the shift in NOSE scores at 6 and 12 months shows a pattern similar to that observed for SNOT-22 scores, that is, the scores tend to improve modestly for medical management, but more markedly for septoplasty at the 6- and 12-month time points.

Measurements of nasal patency

Objective measurements of nasal patency were collected at all three trial visits. The measures collected were PNIF and rhinospirometry measures of MIV and tidal breathing. Measurements were taken both pre and post decongestant, with only the post-decongestant measures presented here. The absolute NPR for MIV and tidal breathing are presented in this section. Summary statistics for the following data are presented in *Appendix 1*:

- PNIF (post decongestant, maximum of three measurements) (*Figure 13*) (see *Appendix 1*, *Table 52*)
- inhaled volume by worse (lower-score) side and better (higher-score) side from post-decongestant MIV rhinospirometry (mean volume from three measurements) (see *Appendix 1*, *Table 53* and *Figure 27*)
- absolute NPR from post-decongestant MIV rhinospirometry (using mean volume from three measurements) (*Figure 14*) (see *Appendix 1*, *Table 54*)
- inhaled volume by worse (lower) side and better (higher) side from post-decongestant, tidal breathing rhinospirometry (one measurement) (see *Appendix 1*, *Table 55* and *Figure 28*).

Absolute NPR measures are defined as the modulus (ignoring the sign) of the NPR, which is calculated in the same way as for the DOASS. The COVID-19 pandemic resulted in the suspension of face-to-face visits, which had a major impact on data collection. Thus, there are limited follow-up data, particularly at 12 months. It is notable that 37 medical management participants underwent NHS surgery after 6 months, whereas only five underwent surgery before the 6-month time point.

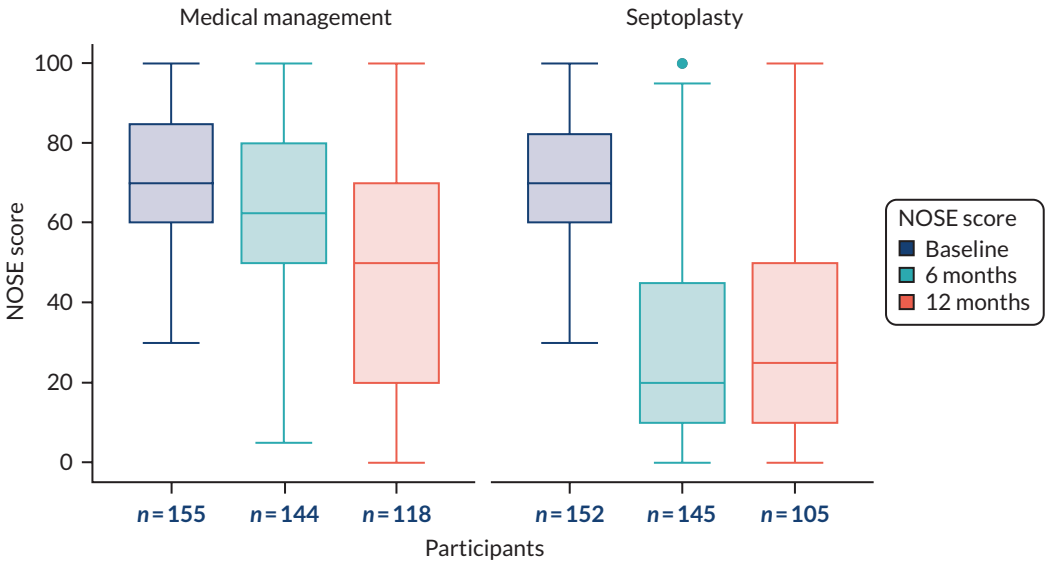

FIGURE 12 The NOSE scores at baseline, 6 months (primary end point) and 12 months, by allocated arm.

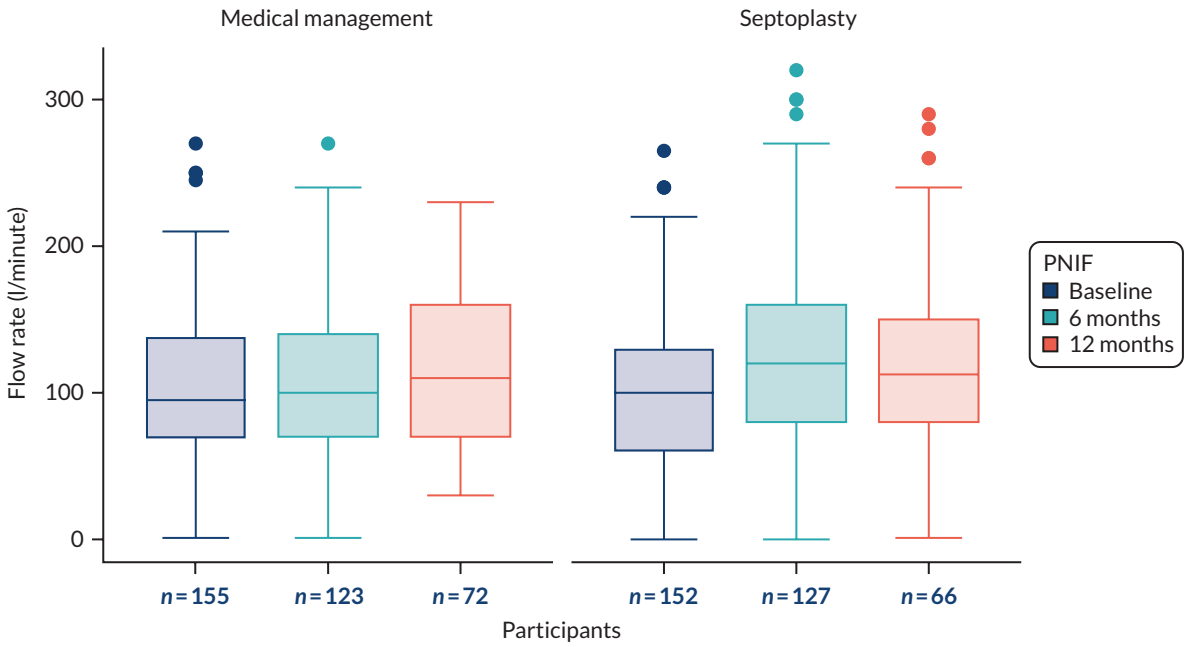

FIGURE 13 Post-decongestant PNIF rate (maximum of three measurements) (ITT population).

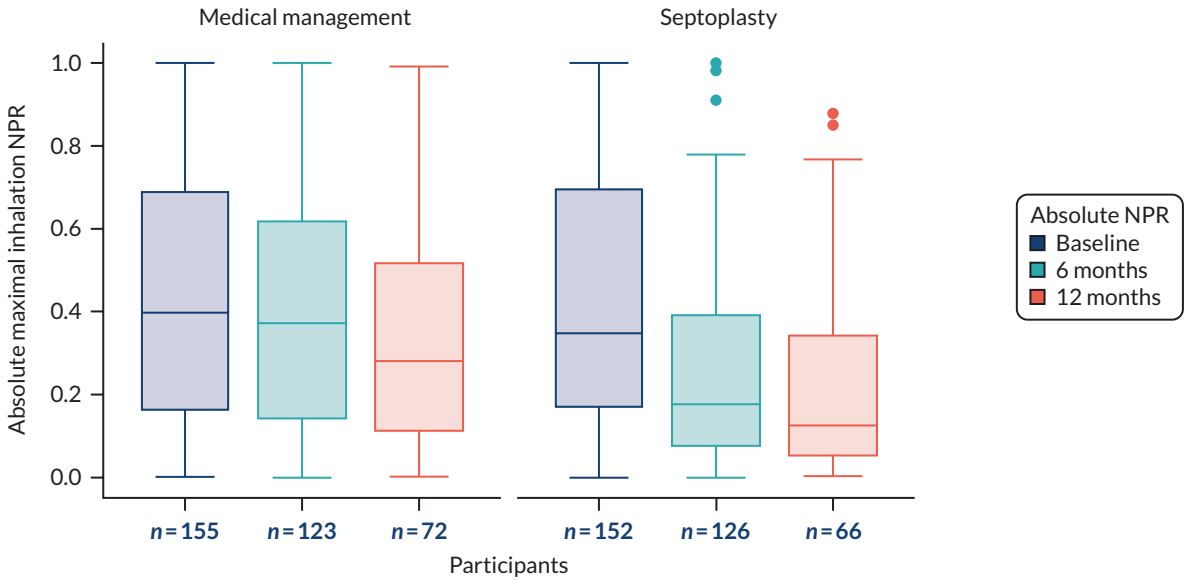

FIGURE 14 Absolute NPR from post-decongestant MIV (using mean volume from three measurements) (ITT population).

Summary statistics of the absolute MIV NPR can be found in *Appendix 1*, *Table 54*. Summary statistics showing raw (volume) data for post-decongestant MIV by better and worse nostril can be found in *Appendix 1*, *Table 53*, with the accompanying box plot in *Appendix 1*, *Figure 27*.

Figure 15 shows the absolute tidal breathing NPR for the ITT population. Summary statistics for the absolute tidal breathing NPR can be found in *Appendix 1*, *Table 56*. Summary statistics showing raw data for post-decongestant tidal breathing by better and worse nostril can be found in *Appendix 1*, *Table 55*, with the accompanying box plot in *Appendix 1*, *Figure 28*.

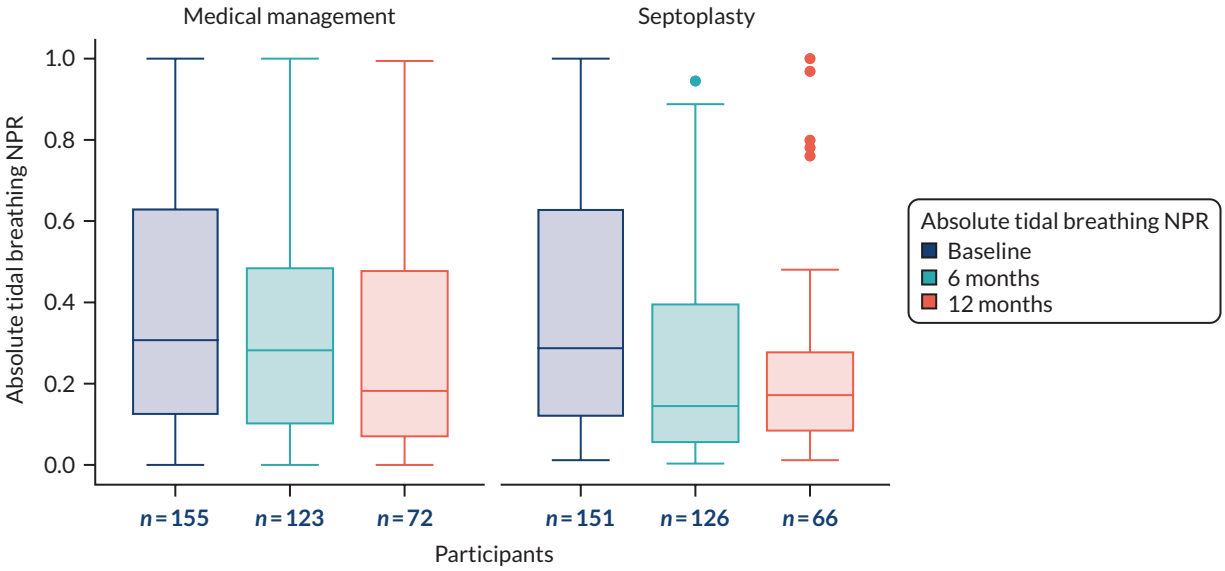

FIGURE 15 Absolute tidal breathing NPR from post decongestant (ITT population).

During the COVID-19 pandemic, face-to-face visits at trial sites were suspended, which meant that fewer participants completed the objective nasal patency outcome measures than had completed the PROMs. Despite the reduction in available data for the objective nasal patency measures, a marked improvement is seen by the 6-month measurement in the septoplasty arm, with a more modest improvement seen in the medical management arm.

Correlation of subjective Double Ordinal Airway Subjective Scale with rhinospirometer measures (maximal inhalation volume and tidal breathing nasal partitioning ratios)

It was in our best interests to discover if physical functional rhinospirometry measurements are necessary to assess patients' nasal obstruction, or if PROMs alone are adequate for such assessments.

Scatterplots of subjective DOASS versus MIV NPR (see *Appendix 1*, *Figure 29*) and versus tidal breathing NPR (see *Appendix 1*, *Figure 30*) were drawn. Spearman's correlation coefficients and 95% CIs about the fitted line are presented for each scatterplot.

The scatterplots use paired data at all time points to assess how well correlated the DOASS is with rhinospirometer measurements.

The correlation and numbers with both measures included in the analyses are as follows:

- The correlation of subjective DOASS to MIV NPR is strong (correlation coefficient = 0.7576; $p < 0.0001$). The number of instances in which both measures are available is 765.
- The correlation of subjective DOASS to tidal breathing NPR is strong (correlation coefficient = 0.7545; $p < 0.0001$). The number of instances in which both measures are available is 762.

Analysis of secondary outcomes

The 12-month SNOT-22 scores, and both the 6- and 12-month NOSE and DOASS scores were analysed in a way similar to that in model 1 (see *Efficacy analysis: primary outcome*). All analyses are for the ITT population, but numbers analysed are reduced owing to lower rates of completion for secondary outcomes.

Table 8 gives the treatment group coefficient of the regression analysis for each secondary outcome placed as the response variable, adjusted for stratification factors (gender and baseline NOSE categories) and the appropriate baseline measure for each secondary outcome, as well as a summary comment highlighting the direction of the effect.

TABLE 8 Summarised results from regression analysis for secondary outcomes

Secondary outcome measure	Participants (*n*)	Regression coefficient for treatment group	95% CI	*p*-value	Direction of effect
SNOT-22 (12 months)	244	−10.073	−14.537 to −5.609	< 0.0001	More favourable outcomes in the septoplasty arm (favours septoplasty)
NOSE					
6 months	289	−33.965	−39.374 to −28.557	< 0.0001	Favours septoplasty
12 months	223	−16.910	−24.200 to −9.620	< 0.0001	Favours septoplasty
Absolute subjective DOASS					
6 months	253	−0.201	−0.251 to −0.150	< 0.0001	Favours septoplasty
12 months	147	−0.101	−0.173 to −0.029	0.006	Favours septoplasty
PNIF (post decongestant)					
6 months	250	16.461	6.339 to 26.533	0.001	Favours septoplasty
12 months	138	13.086	−0.227 to 26.400	0.054	Favours septoplasty
Absolute MIV NPR (post decongestant)					
6 months	249	−0.148	−0.214 to −0.081	< 0.0001	Favours septoplasty
12 months	138	−0.103	−0.186 to −0.019	0.016	Favours septoplasty
Absolute tidal breathing NPR (post decongestant)					
6 months	248	−0.101	−0.165 to −0.037	0.002	Favours septoplasty
12 months	138	−0.075	−0.161 to 0.011	0.088	Favours septoplasty

Participants' opinions of success of the treatment provided

One of the clinical effectiveness aims of the NAIROS trial is to use the results in the surgical arm to explore a possible definition of 'technical failure' in experienced hands, that is experienced surgeons, (i.e. consultants or non-consultant career clinicians, but not trainee otolaryngologists). To explore this, the investigator recorded the participant's satisfaction with the surgery outcome in the post-surgery case report form. Responses were received from 133 out of 166 (80%) of those randomised to receive septoplasty; 116 of the 133 respondents (87%) were recorded as being satisfied and 17 (13%) were recorded as being not satisfied. In addition, for 11 of the medical management participants who requested to receive septoplasty, 10 were recorded as being satisfied and one was recorded as not being satisfied.

To explore the possible relationship between participants' views and surgeons' impressions as to the need for revision surgery, *Table 9* combines responses to the following questions with surgeon opinions:

- At 6 and 12 months, participants were asked by the investigator, 'In the past 6 months do you feel your nasal symptoms have been better than/about the same as/worse than before treatment commenced?'.
- At 6 and 12 months, investigators were asked, 'Will septoplasty or revision septoplasty be required?'. A response of yes/no was recorded. Surgeons could recommend revision surgery if they felt that it was needed.

Only six revision surgeries were recommended for participants randomised to receive septoplasty, four at 6 months and two at 12 months. In one case, the recommendation for revision surgery by the investigator contradicted the participant's view that their symptoms had improved.

TABLE 9 Septoplasty arm: technical fails in terms of participant-assessed improvement and surgeon's opinion on revision surgery requirement

Participant assessment			Surgeon recommended revision surgery (*n*)	
6 months	12 months	Frequency	6 months	12 months
Better at 6 months (*n* = 108)	Better	47	0	0
	Same	11	0	0
	Worse	3	0	0
	Missing	47	1	0
Same at 6 months (*n* = 19)	Better	3	0	0
	Same	9	2	0
	Worse	1	0	0
	Missing	6	1	0
Worse at 6 months (*n* = 7)	Better	2	0	0
	Same	0	0	0
	Worse	3	0	1
	Missing	2	0	0
Missing at 6 months (*n* = 32)	Better	7	0	1
	Same	2	0	0
	Worse	1	0	0
	Missing	22	0	0
Total		166	4	2

Subgroup analyses

Turbinate reduction

At the baseline visit, participants were assessed to determine whether or not it would be appropriate to reduce the inferior turbinate. These assessments are summarised in *Appendix 1*, *Table 57*. The relationship between this recommendation and the occurrence of turbinate surgery is shown in *Appendix 1*, *Table 58*. A subgroup analysis for participants in the septoplasty arm only was carried out.

Of the 155 septoplasties for which information on turbinate reduction was available, 88 (57%) included a turbinate reduction.

Of the 166 septoplasties carried out in the septoplasty arm, 148 have both baseline and 6-month SNOT-22 data, and so could be included in this analysis.

We analysed the data using linear regression adjusting for baseline SNOT-22 score and the stratification factors of severity and gender (*Table 10*). The dependent variable was SNOT-22 score at 6 months, and the model was fitted with the additional binary variable that indicated whether or not the turbinate was reduced in surgery (see *Appendix 1*, *Figure 31*).

The regression analysis shows that, on average, adjusted scores were 2.79 points higher (95% CI −2.78 to 8.35 points; $p = 0.324$) for those who received a turbinate reduction than for those who did not. As turbinate reduction was not a randomised intervention, but a clinical/surgical decision made within the randomised septoplasty, no conclusion can be drawn as to whether this was an effective part of the surgery.

TABLE 10 The SNOT-22 score at 6 months (primary end point), adjusted for baseline SNOT-22 score, stratification factors and turbinate reduction (model 1), ITT population, septoplasty arm only

Model 1	Regression coefficient	SE of coefficient	Test statistic	*p*-value	95% CI coefficient
Turbinate reduced (reference: not reduced)	2.788	2.814	0.99	0.324	−2.776 to 8.352
Baseline SNOT-22 score	0.389	0.076	5.12	< 0.0001	0.239 to 0.539
Gender: male (reference category: female)	−1.307	2.889	−0.45	0.652	−7.019 to 4.405
NOSE severity: severe (reference category: moderate)	−1.773	4.650	−0.38	0.704	−10.968 to 7.422
NOSE severity: extreme (reference category: moderate)	−1.139	5.212	−0.22	0.827	−11.445 to 9.168
Constant	2.819	5.177	0.54	0.587	−7.419 to 13.057

SE, standard error.

Note
n = 142, adjusted R^2 = 0.1911 probability ≥ F ≤ 0.0001.

Subpopulation treatment effect pattern plot by baseline Nasal Obstruction Symptom Evaluation score

Figure 16 shows the STEPP for the ITT population, demonstrating the impact of baseline NOSE score on the primary outcome (i.e. SNOT-22 score at 6 months).

The green line with shaded 95% CI limits in *Figure 16* shows the average effect of being randomised to septoplasty for those with specific NOSE scores at baseline. For those with moderate NOSE scores at baseline, the average improvement in SNOT-22 score is around 5 units. Those with scores of around 60 have an average improvement of around 15 units, and those with extreme scores at baseline can improve by as much as 30 units. All of the values covered by the green line show improvements in SNOT-22 scores. However, it is clear that improvement increases as baseline severity increases.

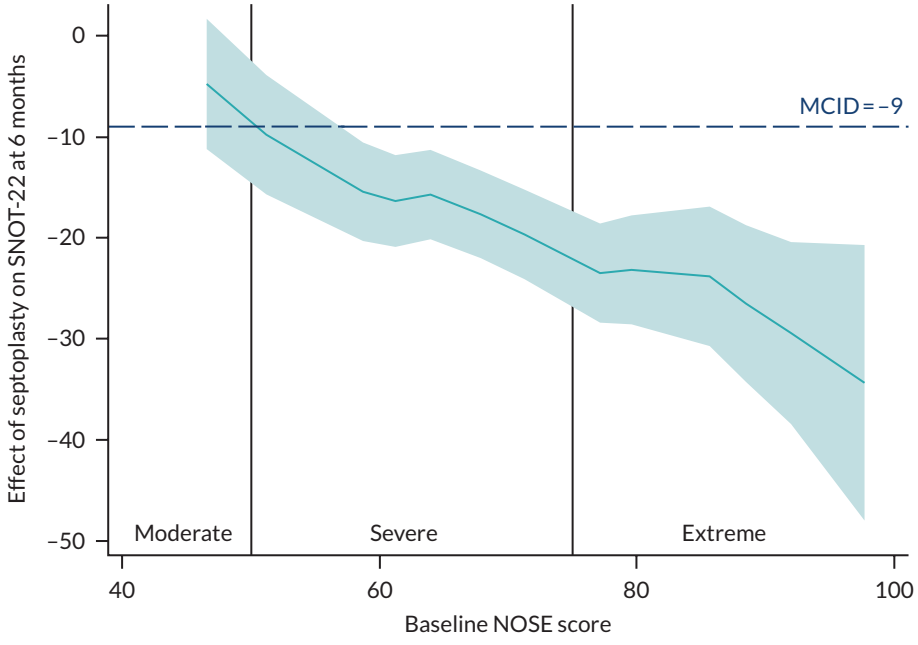

FIGURE 16 The STEPP of all participants in the ITT population.

It is important to consider the 'floor' effect of the SNOT-22 variable, which means that participants with SNOT-22 scores of < 20 at baseline have limited scope for improvement.[96] Baseline SNOT-22 scores ranged from 6 to 104 (see *Table 5*), with 75% of scores being ≥ 27 and hence well above the impact of the floor effect.

A STEPP analysis of SNOT-22 scores at 6 months by DOASS (worse side at baseline) did not show a reportable trend between the two variables (see *Appendix 1*, *Figure 32*).

Analysis by gender

A subgroup analysis of the primary outcome by gender was performed. This is reported using paired data to assess individual changes in SNOT-22 scores from baseline to 6 months, and baseline to 12 months (presented in *Appendix 1*, *Table 59*; see *Figure 33* for corresponding box plots). As part of the subgroup analysis by gender, STEPPs were produced separately for males and females [see *Appendix 1*, *Figures 34* (male) and 35 (female)]. No major differences between gender were observed.

Safety

Adverse events

A total of 227 AEs were reported across 123 unique participants. Differentiated by arm, this equates to 95 AEs reported by 62 unique participants in the medical management arm and 132 AEs reported by 61 unique participants in the septoplasty arm. The severity of reported AEs is tabulated in *Appendix 1*, *Table 60*. The action taken to address the AEs is tabulated in *Appendix 1*, *Table 61*, which shows that 61% of AEs required no action, 11% required that treatment be interrupted or discontinued and 28% were treated with concomitant medications. The status of the AEs (ongoing or resolved) at the end of the trial is tabulated in *Appendix 1*, *Table 62*. This table shows that 66% of AEs were categorised as resolved, 26% were categorised as ongoing and the other 8% were categorised as 'resolving'. *Appendix 1*, *Table 63*, summarises causality and severity for the AEs by randomised arm.

Three participants randomised to septoplasty had an AE date after the end of follow-up in the ITT population. Two were within the compliance window for the 12-month visit and one was beyond the compliance window (see *Appendix 1*, *Table 64*).

AE start dates were not recorded for six participants; however, their AE completion dates are provided (see *Appendix 1*, *Table 65*). Line listings of the 227 AEs for all participants can be found in *Appendix 1*, *Table 66*. As the AE event terms were reported as free text in the database, these subsequently underwent Medical Dictionary for Regulatory Activities (MedDRA) coding. *Table 11* presents a summary of the AEs, categorised according to approximate lowest-level MedDRA term.

Serious adverse events

There were 23 SAEs reported by 16 unique participants. Differentiated by arm, this equates to nine SAEs reported by five unique participants in the medical management arm and 14 SAEs by 11 unique participants in the septoplasty arm.

Serious AE causality and severity by randomised arm is summarised in *Appendix 1*, *Table 67*; *Appendix 1*, *Table 68*, groups the SAEs by both category and severity. *Figure 17* shows the timings of SAEs; many of these correspond with the timing of septoplasty.

Table 12 shows the SAEs recategorised by the clinical team. A line listing of the 23 SAEs is presented in *Appendix 1*, *Table 69*. The median time from septoplasty to SAE is 0 days and the maximum time is 8 days.

There were four reported SUSARS: four mild events in the septoplasty arm that were related to septoplasty. These are shown in the last column in *Appendix 1*, *Table 69*.

TABLE 11 Summary of AE MedDRA categories by randomisation arm

AE category by lowest-level MedDRA term	Trial arm (*n*)		Total (*n*)
	Septoplasty	Medical management	
Nasal pain	19	5	24
Other pain	12	7	19
Nasal-induced infection/fever/temperature	11	7	18
Infection/fever/temperature	11	8	19
Epistaxis/bleeding/clot	13	20	33
Rhinorrhoea/mucus	9	5	14
Cough/cold/influenza	9	5	14
Headache	2	6	8
Dry nose/itching/crusting	1	6	7
Blocked nose	6	0	6
Numbness	4	1	5
Nose shape/asymmetry	4	0	4
Reflux/heartburn	0	4	4
Ear blocked/tinnitus/labyrinthitis	3	0	3
Anxiety/depression	0	3	3
Swelling	3	0	3
Dizziness	2	0	2
Nausea	1	1	2
Perforation	2	0	2
Sense of smell/taste	2	0	2
Adhesion/synechiae	1	0	1
Tiredness/fatigue	1	0	1
Other	15	17	33
Total	132	95	227

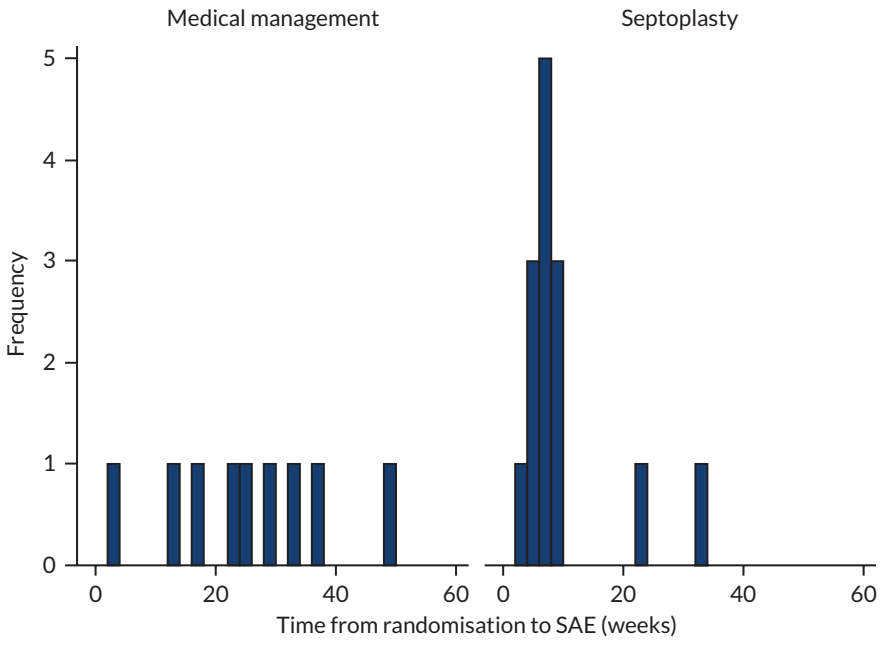

FIGURE 17 Time from randomisation to SAE start date.

TABLE 12 Serious AEs by randomisation arm, recategorised by the clinical team

Categorised SAE	Trial arm (*n*)		Total (*n*)	SUSAR[a]
	Septoplasty	Medical management[a]		
Anaesthetic complication	3[a]	2	5	3
Infection	2	2	4	
Postoperative bleeding	5[a]	1	6	1
Vasovagal episode	2	0	2	
Polypharmacy overdose	0	3	3	
Trauma unrelated to the trial	0	1	1	
Inappropriate hospital admission[b]	2	0	2	
Total	14	9	23	

a Serious AEs in the medical management arm were not related to trial surgical interventions.
b Admitted overnight in error.

Surgical complication/failure and reintervention within 12 months

Participants allocated to either trial arm who received trial or non-trial septoplasty at any point during the trial were asked to report AEs at 6 and 12 months; 174 participants responded. The numbers of participants who responded (yes/no) to the specific questions about complications at either or both of these time points are summarised in *Table 13*. Participants could also report 'other' complications. These are listed in *Appendix 1*, *Table 70*. Complications that could not be coded in specific categories in *Table 13* were classified as 'other' complications.

The 'other surgery complications' were assessed by the chief investigator and a TMG clinician. Three were recategorised and are included in *Table 13* in the relevant categories. Nine of these were not deemed to be complications and are not included in *Table 13*, leaving seven other complications which are listed in *Appendix 1*, *Box 1*. One complication is related to adhesions, and so is included in *Table 13*. Total unique participant numbers vary owing to incomplete data collection. *Table 13* also summarises the total reports of adhesions and perforations that occurred by randomised arm. One adhesion and two perforations were reported as AEs, but were also listed in the clinical exam electronic case report form (eCRF).

TABLE 13 Surgical complications reported at 6 and 12 months

Complication	Frequency	Unique participants (*n*)	Rate (frequency ÷ *n*) (%)
Bleeding nose necessitating re-admission to hospital	7	174	4
Infection requiring antibiotic treatment	20	172	12
Decrease in sense of smell	19	171	11
Numbness of upper teeth	18	171	11
Change in the appearance of the nose	17	171	10
Other surgery complications[a]	7	173	4
Adhesions[a]	7	179	4
Perforations[a]	6	179	3

a These were assessed by clinical examination.

Summary of key findings

- The trial recruited to target; primary outcome data are available for 81% of participants.
- There is strong evidence that randomisation to the septoplasty arm reduces a participant's SNOT-22 score by approximately 20 units more than randomisation to the medical management arm at 6 months.
- At 12 months, the larger reduction in SNOT-22 score in the septoplasty arm, compared with the medical management arm, is sustained but diminished to 10 units; this is still a statistically significant difference.
- All sensitivity analyses confirm that the message of the primary outcome is a strong and consistent signal, with similar improvements seen in all secondary outcomes.
- The STEPPs show that the more severely symptomatic a participant is at baseline, the larger a reduction in SNOT-22 scores they should expect from the septoplasty.
- Nineteen out of 23 SAEs were related to septoplasty undertaken in either arm of the trial. No participants required return to theatre for bleeding or infective reasons in the short term. NAIROS-reported complications were those recognised in the septoplasty/turbinate reduction literature.

Chapter 4 Economic evaluation

This chapter reports the economic evaluation conducted as part of the NAIROS trial, which included both a within-trial analysis and a longer-term model-based analysis.

Within-trial analysis

Introduction

The question addressed by the within-trial analysis was as follows: for adults experiencing nasal obstruction associated with a deviated septum, what is the cost-effectiveness of surgical management compared with medical management at 12 months?

The within-trial analysis included a cost-effectiveness analysis (CEA) and a cost–utility analysis (CUA). The CEA estimated the incremental cost per improvement in SNOT-22 score (defined as a change of ≥ 9 points, as outlined in *Chapter 2*, *Sample size calculation*) and the incremental cost per AE avoided. The CUA estimated the incremental cost per QALY gained. For the CUA, responses to the SF-36 were converted into SF-6D utility scores using standard algorithms; these were then used to estimate QALYs[82] using the area under the curve approach.[83] As costs and effects were reported for 12 months, they were not discounted in the within-trial analysis.

For the within-trial analysis, the following outcomes are reported:

- NHS/PSS costs of managing individuals with nasal airway obstruction associated with a deviated septum
- direct and indirect costs to participants from nasal airway obstruction associated with a deviated septum
- changes in the SNOT-22 score at 6 and 12 months post randomisation l total number of AEs at 12 months post randomisation
- QALYs based on responses to the SF-36, administered at baseline and at 6 and 12 months post randomisation
- incremental cost-effectiveness ratios (ICERs) –
    - incremental cost per improvement (of ≥ 9 points) in SNOT-22 score
    - incremental cost per AE avoided
    - incremental cost per QALY gained.

Methods

This analysis was designed and conducted according to best practice, conforming to the Consolidated Health Economic Evaluation Reporting Standards.[97] All analyses were undertaken using Stata version 16. All economic analyses were based on an ITT principle.

Cost data collection

The economic evaluation was conducted from the perspectives of the UK NHS and PSS. Costs were in 2020 Great British pounds. Data on resource use, use of services, and time away from usual activities were combined with trial-specific estimates and nationally available data to produce a total cost for each trial participant.[98,99]

Details of surgical treatment (septoplasty) were recorded on eCRFs and follow-up healthcare resource use data were collected via a specifically designed HUQ (see *Report Supplementary Material 4*), administered at 6 and 12 months post randomisation. The HUQ is a bespoke questionnaire used in previous studies that was adapted for this study[100,101] based on input from the TMG and PPI. Medications received were

collected in the concomitant medication eCRF, which was completed 2 weeks post randomisation or 2 weeks post surgery, depending on the randomised allocation, and at 6 and 12 months post randomisation. The collection of these healthcare costs allowed us to determine the average total cost of managing an individual with nasal airway obstruction associated with a deviated septum to the NHS.

Sensitivity analyses took a broader perspective that considered individual participant costs. Participant costs were collected in the HUQs and the time and travel questionnaire (see *Report Supplementary Material 4 and 5*). Similar to the HUQ, the time and travel questionnaire is a bespoke questionnaire that was adapted for this study.[100,101] The time and travel questionnaire was administered 12 months post randomisation. Both questionnaires identified direct (e.g. out-of-pocket purchase of pain medication) and indirect (e.g. time off paid work/usual activities) costs to participants.

Intervention costs

Participants were randomised to receive either surgery (septoplasty) or medical management (two different nasal sprays used concomitantly for 6 months) for their nasal airway obstruction.

Septoplasty with or without turbinate reduction

The NHS day-case tariff for septoplasty (CA11A) was used in the base-case analysis (see *Appendix 2*, *Table 71*). Every participant reported to have received septoplasty during the 12-month follow-up was assigned this cost. It was assumed that those who were lost to follow-up and had not yet received surgery did not receive septoplasty. In a sensitivity analysis, costs associated with surgery were estimated using microcosting.[102]

For the microcosting exercise, the cost of each surgery was based on information provided in the eCRF, taking into account the mix of staffing, overheads, and consumable and reusable resources required.[102] The duration of admission was estimated using the number of nights in hospital reported in the eCRF. Reusable and consumable resources were based on resources needed to undertake a septoplasty; additional resources were assigned if turbinate reduction was performed. Reusable and consumable resources were identified using personal communication with clinical staff (Sean Carrie and Graham Stobbs, The Newcastle upon Tyne Hospitals NHS Foundation Trust, 8 April 2021, personal communication) and are detailed in *Appendix 2*, *Table 72*. Staff costs reflected the grade of the senior operating surgeon and senior anaesthetist recorded on the eCRF. In addition to the staff recorded on the eCRF, the number, type and grade of all other staff routinely present were identified based on clinical advice (Sean Carrie and Graham Stobbs, personal communication). Based on this advice, we also accounted for the presence of a scrub nurse, floor nurse, healthcare assistant, operating department practitioner and anaesthetic specialist registrar. The length of time in the operating theatre was estimated by deducting the time in the operating room from the time out of the operating room recorded on the eCRF. The name, dose, frequency and duration of any discharge medication were identified from the eCRF.

The unit costs of consumable and reusable resources identified during the microcosting process were sourced using information from the Newcastle site (Graham Stobbs, The Newcastle upon Tyne Hospitals NHS Foundation Trust, 1 September 2021, personal communication), and are detailed in *Appendix 2*, *Table 72*. Staff salaries, inpatient stays and discharge medication were costed from routine sources.[103–105]

The surgery eCRF was completed for participants randomised to septoplasty who had surgery; it was not completed for participants randomised to medical management who then went on to have septoplasty. Therefore, total surgery costs based on microcosting estimates were calculated only for those randomised to septoplasty who received septoplasty. These surgery costs were aggregated to estimate an average total cost for septoplasty, which was assigned to participants in both arms who received surgical management.

Medical management

All participants randomised to medical management were provided with nasal sprays, which were to be used daily for 6 months. Regardless of compliance, the costs associated with providing these nasal sprays to participants was assumed. Participants were provided with five of the Stérimar nasal spray

canisters and 11 of the mometasone nasal spray bottles. The cost of these nasal sprays was obtained from routine sources (see *Appendix 2*, *Table 71*).[106]

All information on the interventions received was used to estimate the total intervention resource use and total intervention cost per participant for each randomised arm. These estimates were presented as average total resource use and average total intervention cost per participant per arm.

Healthcare costs (excluding intervention costs)

The 6-monthly HUQs captured information on the type and frequency of primary and secondary care resource use at 6 and 12 months post randomisation. Primary care resources included visits with a GP, visits with a nurse, and 'other health professional' consultations. Participants were asked to provide details on 'other health professionals'. Primary care consultations could take place at the healthcare provider's practice, at the participant's home or over the telephone (including telephone calls to NHS call centres). Secondary care resources included visits to an accident and emergency (A&E) department, outpatient clinics and hospital admissions (day patient or overnight).

Participants could also report additional medications to manage their nasal obstruction; this information was collected in the concomitant medication eCRF.

All information on healthcare contacts and medications are presented as the average total number of participants who used each healthcare service, and the average total number of visits for each healthcare resource use at each time point per arm.

The costs associated with each of these healthcare contacts and medications were collected from routine sources[98,99,102] and combined with the frequency of resource use to estimate the total healthcare cost for each participant and the average total cost per participant per arm (see *Appendix 2*, *Table 71*).

Participant costs

Participant costs were included as a sensitivity analysis. Direct and indirect costs to participants were captured via both the HUQ and the time and travel questionnaire. The HUQ collected information on out-of-pocket payments for private health care or personal care. The HUQ also collected information on time away from usual activities owing to illness to capture the opportunity cost of participants' time.

The time and travel questionnaire collected additional participant costs. These were the direct and indirect costs associated with attending healthcare appointments. The questionnaire captured information on how participants travelled to each type of healthcare appointment (including out-of-pocket expenses), how much time they spent at each type of appointment, what they would otherwise have been doing and whether they were alone or accompanied by someone else. All information on participant costs for each type of healthcare appointment was summarised as average totals per participant.

Unit costs to derive participant costs were collected from routine sources and from the time and travel questionnaire (see *Appendix 2*, *Table 71*). The cost associated with time off paid work was estimated using the median national wage rate.[107] The unit cost for time away from usual activities was based on non-working time reported by the Department for Transport.[108] Travel costs were derived based on the mode of transportation reported. Mileage rates were estimated based on rates reported by the Automobile Association.[109] Parking costs or public transport fares were reported in the time and travel questionnaire. Time and travel costs were summarised for each type of healthcare appointment to estimate a unit cost for each face-to-face healthcare appointment. These unit costs were combined with the number of visits reported in the HUQs to estimate the average total cost per participant.

Adverse event costs

Information on AEs and SAEs was collected via the AE eCRF completed 2 weeks post randomisation, 2 weeks post surgery and throughout the follow-up period. Some AEs may have resulted in additional

medications or hospitalisation. In the base-case analysis, the costs of AEs, medication and/or hospitalisation were excluded to prevent double-counting. It was assumed that any medications received were reported on the concomitant medication form. It was also assumed that any AEs resulting in hospitalisation were captured in the HUQ. The frequency of medications and hospitalisations reported in the AE eCRF was compared with responses to the concomitant medication eCRF and the HUQ. If more medications and/or hospitalisations were reported in the AE eCRF, then the cost of these resources was incorporated in a sensitivity analysis. The costs of these hospitalisations and medications were obtained from routine sources[103,105] and were assigned to each AE hospitalisation and medication to estimate the average total AE cost per participant.

To summarise, data collection on resource use and costs can be split into:

- interventions costs (surgery and nasal sprays) collected via eCRFs
- treatment costs collected via the HUQ and the concomitant medication form
- participant costs collected via the HUQ and the time and travel questionnaire.

Estimation of effects

Three effectiveness measures were used in this economic evaluation: nasal function measured by SNOT-22 score, number of AEs, and QALYs based on responses to the SF-36.

Estimation of health outcomes for the cost-effectiveness analysis

Two different outcome measures were used in the CEA:

1. improvement in SNOT-22 score at 6 and 12 months post randomisation
2. number of AEs.

First, we used nasal function, measured by the SNOT-22 administered at baseline and at 6 and 12 months post randomisation, as a measure of effectiveness. A clinically significant change in SNOT-22 scores was defined as a difference of ≥ 9 points (see *Chapter 2*, *Statistical considerations*). The individual SNOT-22 scores were derived by the statistical team as previously outlined (see *Chapter 2*, *Analysis of the primary outcome*). The change in SNOT-22 score between baseline and 12 months was estimated for every participant and presented as the average total proportion of participants who had an improvement in SNOT-22 scores (i.e. a difference of ≥ 9 points) per arm. This analysis was replicated to identify the difference in SNOT-22 scores between baseline and 6 months for every participant.

The second measure of effectiveness was the number of AEs reported in each arm.[110,111] The total number of AEs was aggregated for each participant and presented as the average total number of AEs per arm.

Estimation of quality-adjusted life-years for the cost–utility analysis

The SF-36 was administered at baseline and at 6 and 12 months post randomisation. The SF-36 is a practical, reliable and valid measure of physical and mental health.[112] The responses to the SF-36 were converted into the SF-6D, a preference-based utility index, using a standard algorithm to produce a health-state utility score.[82] The SF-6D comprises six multilevel dimensions: physical functioning, role limitations, social functioning, bodily pain, mental health and vitality. The area under the curve approach was used to assign time weighting to the utility scores. The time-weighted average of the scores based on the responses to the SF-36 throughout the follow-up period allowed us to generate QALY values for each participant. *Equation 1* is an illustrative example of how QALYs were estimated:

$$\text{QALY} = (\text{utility}_{\text{baseline}} + \text{utility}_{\text{6months}}) \div [2 \times 6/12] + (\text{utility}_{\text{6months}} + \text{utility}_{\text{12months}}) / [2 \times 6/12]. \quad (1)$$

Comparative incremental analyses of costs and outcomes between trial arms

Unadjusted and adjusted (regression) analyses were performed to estimate the cost-effectiveness of septoplasty compared with medical management. All results were presented as point estimates of the mean incremental costs, effects and cost-effectiveness.

The cost-effectiveness plane (*Figure 18*) illustrates how a decision is made based on the economic results. The difference in QALYs is shown on the x-axis and the difference in costs is shown on the y-axis. At the origin there is no difference in costs and effects between the two management strategies. If septoplasty was found to be both less costly and more effective (south-east quadrant), it would be dominant and would be considered cost-effective. If septoplasty was found to be both more costly and less effective (north-west quadrant), medical management would be dominant and septoplasty would not be considered cost-effective. If septoplasty was found to be more effective, but more costly, or less effective and less costly (north-east and south-west quadrants, respectively), then we would have to consider which management strategy is more likely to be cost-effective. In this situation, decisions were based on the ICER, which estimates the cost per additional unit of effect (i.e. the difference in costs divided by the difference in effects between the two arms). In this situation the ICER is compared with the threshold value society places on an additional unit of effect, if there is one available (the additional unit of effect is illustrated by 'a', the dotted line in *Figure 18*).

Cost–effectiveness analysis

In the base-case analysis, the CEA was based on the incremental cost per additional participant who had an improvement in SNOT-22 score at 12 months post randomisation. In sensitivity analyses, the measure of effectiveness was changed to (1) incremental cost per additional participant who had an improvement in SNOT-22 score at 6 months post randomisation and (2) incremental cost per AE avoided at 12 months post randomisation (see *Sensitivity analysis* for further details). The average total cost and average total proportion of participants who had an improvement in SNOT-22 scores were estimated for each management strategy. These were presented as point estimates of mean incremental costs and effects and the incremental cost per additional participant who had an improvement in SNOT-22 score. If there was no dominant management strategy, the ICER would be difficult to interpret (as there is no threshold value for an improvement in SNOT-22 score with which to compare the ICER) hence the need for the CUA.

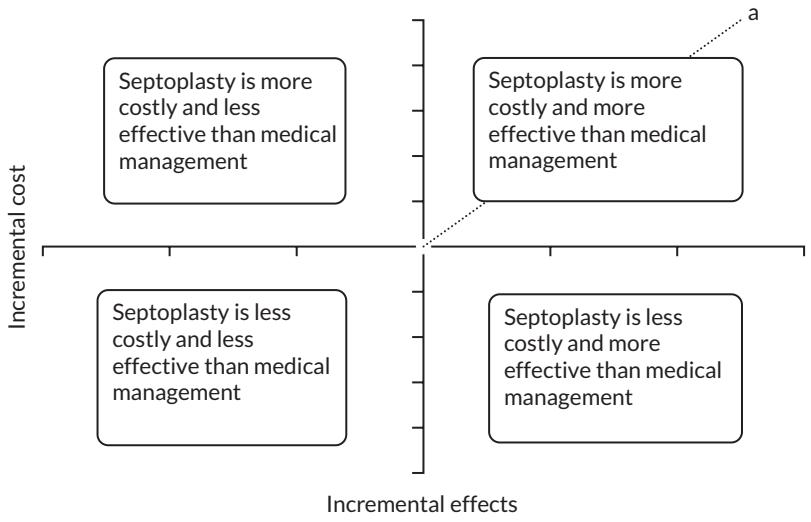

FIGURE 18 Cost-effectiveness plane. a, Society's threshold to pay for one more unit of effect.

Cost–utility analysis

The CUA was based on the incremental cost per QALY gained. The average total cost and average total QALYs were estimated for each arm and presented as point estimates of mean incremental costs and effects (QALYs) and the incremental cost per QALY gained. This can be compared with a decision-makers' threshold value. For example, a typical threshold for an additional QALY in England, according to the National Institute for Health and Care Excellence (NICE), is approximately £20,000.[113]

Adjusted analysis: seemingly unrelated regression

We adjusted our analyses, using seemingly unrelated regression (SUR)[114] to estimate the difference in cost-effectieveness between the two management strategies. SUR permits the simultaneous estimation of costs and effects, calculated at individual level, while accounting for unobserved individual characteristics that could affect both costs and effects and lead to potential correlation between these two variables.[115] In addition, the SUR allowed us to control for additional covariates (age, gender, ethnicity, baseline SNOT-22 score and baseline utility scores) that may have affected costs and/or effects.

Sensitivity analysis

It was anticipated that there would be missing responses to the participant questionnaires (the HUQ and the SF-36). In the base-case analysis, missing data were imputed using chained multiple imputation methods.[116] Chained multiple imputation makes multiple predictions for missing cost and effect data simultaneously.[117] Data were assumed to be missing at random. Differences in baseline characteristics, including baseline utility, between participants with missing and participants with complete data were undertaken using t-tests to validate this assumption.

Sensitivity analyses were conducted to assess the robustness of the base-case results to realistic variations in the levels of underlying data. The following deterministic sensitivity analyses were used in the base-case analysis:

- CEA sensitivity analyses –
    - the measure of effectiveness was improvement in the SNOT-22 score from baseline to 6 months
    - the measure of effectiveness was the number of AEs.
- CUA sensitivity analyses –
    - surgery costs were estimated using microcosting and compared with the NHS tariff
    - participant costs included
    - costs and QALYs were estimated for all participants with complete data only (i.e. no imputations for missing data)
    - the eligibility criteria were changed and the base-case CUA was run for participants who had a severe or extreme baseline NOSE score only
    - incremental cost per QALY at 6 months.

Stochastic sensitivity analysis, using the bootstrapping technique,[118] explored the impact of the statistical imprecision surrounding estimates of costs, effects and cost-effectiveness. The bootstrapped results are presented on a cost-effectiveness plane (see *Appendix 2*, *Figure 36*) and used to illustrate the distribution of incremental costs and incremental effects from which we can identify the uncertainty in our results.[119]

The bootstrapped results were also presented as cost-effectiveness acceptability curves (CEACs) (see *Appendix 2*, *Figure 37*). CEACs allow us to identify the management strategy that maximises net benefits at each threshold value for an additional unit of health effect (i.e. an improvement in SNOT-22 scores, AEs avoided and QALYs gained).[120]

Results

Data validity and completeness

The response rates to participant questionnaires (the HUQ and the SF-36) used to inform the economic analysis are presented in *Appendix 2*, *Table 73*. There was a decline in response to the participant questionnaires over the 12-month follow-up period. Slightly fewer participants in the septoplasty arm responded to the participant questionnaires at 6 and 12 months than at baseline. The overall response rates were 66% for the HUQ and 68% for the SF-36. There was no difference in baseline characteristics or utilities between responders and non-responders [mean differences: age −3.15 (p = 0.0787), gender −0.04 (p-value = 0.5329), baseline utility −0.010 (p-value = 0.5768)], so we assumed that data were missing at random.

Resource use and costs

Over the 12-month follow-up, participants reported contacts with various healthcare providers in primary and secondary care settings. On average, participants in both arms reported similar healthcare contacts, with visits to a GP being the most frequently reported contact for both arms. Further details are provided in *Appendix 2*, *Table 74*.

Details on unit costs, which were combined with healthcare contacts, are provided in *Appendix 2*, *Table 71*. On average, participants reported similar healthcare costs at 6 and 12 months, which was expected given the resources reported in *Appendix 2*, *Table 74*. Medications prescribed during the follow-up are listed in *Appendix 2*, *Table 75*. Primary and secondary healthcare costs could be estimated for 66% of participants (n = 204). After these costs were combined with the intervention costs (septoplasty and nasal sprays) and medication costs, septoplasty was, on average, more costly at 12 months than medical management (mean difference £1277, 95% CI £1068 to £1487; $p < 0.01$). This difference in average total costs was maintained when missing cost data were imputed (mean difference £1189, 95% CI £1014 to £1363; $p < 0.01$). *Table 14* presents the average total cost for each arm by cost category.

TABLE 14 Average total costs at 12 months by randomised arm

Cost	Medical management (N = 155)		Septoplasty (N = 152)		Mean difference[a] (95% CI) (£)
	Participants providing data (n)	Mean (SD)	Participants providing data (n)	Mean (SD)	
Surgery costs[b]	155	593 (902)	152	1905 (314)	
Discharge medications	9	8 (7)	123	8 (7)	
Nasal spray costs	155	91 (0)	152	0 (0)	
HUQ costs					
At 6 months	142	134 (238)	140	156 (157)	
At 12 months	115	143 (168)	99	97 (128)	
Total	109	261 (292)	95	276 (234)	
Medication costs	63	8 (15)	84	16 (32)	
Total costs	109	930 (980)	95	2207 (358)	1277 (1068 to 1487)
Total costs: multiple imputation	155	973 (1028)	152	2162 (375)	1189 (1014 to 1363)

a Mean differences were estimated using t-tests.
b Surgery costs were estimated using NHS tariff.[105]

Microcosting

In the septoplasty arm, 148 participants underwent the procedure and provided data on the eCRF for the microcosting exercise. Details of the resources used to undertake septoplasty for these participants are reported in *Appendix 2*, *Table 72*. On average, the length of time in theatre was 57 minutes and 99% of participants had septoplasty ± inferior turbinate reduction.

Participant costs

Participants' time away from usual activities (including work) owing to illness is presented in *Appendix 2*, *Table 74*. On average, participants randomised to septoplasty reported more time away from usual activities at 6 months than those in the medical management arm (mean difference 1.09 days; $p = 0.38$). However, at 12 months, participants in the septoplasty arm reported, on average, fewer days away from usual activities (mean difference −2.39 days; $p = 0.1155$).

Private healthcare use is summarised in *Appendix 2*, *Table 76*. The majority of costs reported were not related to the participants' deviated septa and were not included in further analysis.

Responses to the time and travel questionnaire are summarised in *Appendix 2*, *Table 77*.

Effectiveness outcomes

Summaries of all effectiveness measures by randomised arm are presented in *Table 15*.

Estimation of health outcomes for the cost-effectiveness analysis

On average, a greater proportion of participants randomised to septoplasty than to medical management reported improved nasal function (measured as an improvement of ≥ 9 points in SNOT-22 scores) at 6 and 12 months, compared with baseline scores [mean difference at 6 months 0.42 (95% CI 0.32 to 0.52; $p < 0.01$), mean difference at 12 months 0.25 (95% CI 0.13 to 0.37; $p < 0.01$)].

On average, participants randomised to septoplasty reported more AEs than those randomised to medical management at 12 months (mean difference 0.29, 95% CI 0.02 to 0.57; $p = 0.0382$).

TABLE 15 Summaries of outcome measures used in the CEA and CUA, by randomised arm

	Medical management (*N* = 155)		Septoplasty (*N* = 152)		
Outcome measure	Participants providing data (*n*)	Mean (SD)	Participants providing data (*n*)	Mean (SD)	Mean difference (95% CI)
Improvement in SNOT-22 score					
At 6 months	155	0.381 (0.49)	152	0.803 (0.40)	0.422 (0.32 to 0.52)
At 12 months	125	0.504 (0.50)	119	0.756 (0.43)	0.252 (0.13 to 0.37)
Number of AEs	155	0.54 (0.90)	152	0.84 (1.50)	0.294 (0.02 to 0.57)
SF-6D utility scores					
At baseline	152	0.712 (0.14)	149	0.715 (0.14)	
At 6 months	140	0.729 (0.14)	140	0.789 (0.14)	
At 12 months	117	0.742 (0.16)	103	0.777 (0.14)	
QALYs	111	0.741 (0.13)	99	0.761 (0.13)	0.021 (−0.01 to 0.06)
QALYs: multiple imputation	152	0.727 (0.12)	149	0.766 (0.12)	0.040 (0.01 to 0.07)

a Mean differences were estimated using *t*-tests.

Estimation of quality-adjusted life-years for the cost–utility analysis

On average, participants reported their health status, measured by the SF-6D, as being less than perfect throughout the trial follow-up period. At baseline, participants in both arms reported having a similar health status and both reported improvements in their health status over the trial period. However, on average, those randomised to septoplasty reported greater improvements in their health status at 6 and 12 months post randomisation than those in the medical management arm. Participants in the septoplasty arm also reported more QALYs at 12 months (mean difference 0.02, 95% CI −0.01 to 0.06; $p = 0.235$) than those in the medical management arm. This difference in QALYs increased when missing SF-6D data were imputed (mean difference 0.04, 95% CI 0.01 to 0.07; $p < 0.01$).

Economic evaluation

Incremental cost-effectiveness analysis

Table 16 presents the unadjusted average total costs and average total proportion of participants who reported an improvement in nasal function measured using the SNOT-22 per randomised arm at 12 months. On average, septoplasty was more costly and more effective than medical management. Adjusted analyses were used to estimate incremental costs and effects; these estimates were used to estimate the ICER. The incremental cost for an improvement of ≥ 9 points in SNOT-22 score per participant was £4855. As the threshold value placed on an improvement in SNOT-22 score increases, so does the probability of septoplasty being considered cost-effective.

The results of the stochastic sensitivity analysis are presented in *Figures 19* and *20*. *Figure 19* is the cost-effectiveness plane; for all of the bootstrapped iterations, septoplasty was more costly and more effective than medical management. *Figure 20* is the CEAC and shows that, as the value placed on an additional participant's SNOT-22 score improving by ≥ 9 points in SNOT-22 score increases, so does the probability of septoplasty being considered cost-effective.

Incremental cost–utility analysis

Table 17 presents the unadjusted average total costs and average total QALYs per randomised arm at 12 months. On average, septoplasty was more costly and more effective than medical management. Adjusted analyses were used to estimate incremental costs and effects; these estimates were used to estimate the ICER. The incremental cost per QALY gained was £27,114. Similar to the CEA results, as the value placed on the additional benefit of septoplasty increased, so did the probability of septoplasty being considered cost-effective. Assuming a £20,000 threshold, septoplasty had a 15% probability of being considered cost-effective, which increased to 68% as the threshold increased to £30,000 at 12 months.

The results of the stochastic sensitivity analysis are presented in *Appendix 2*, *Figures 36* and *37*. In all of the bootstrapped iterations, septoplasty was more costly and more effective than medical management. The majority of the bootstrapped iterations are above the £20,000 NICE threshold.[113] The CEAC illustrates that, as the value placed on an additional QALY increases, so does the probability of septoplasty becoming cost-effective.

Sensitivity analysis

Cost-effectiveness sensitivity analyses

The measure of effectiveness was improvement in the Sino-nasal Outcome Test-22 items score from baseline to 6 months When costs and improvement in SNOT-22 scores were estimated at 6 months, septoplasty was, on average, more costly and more effective than medical management (see *Appendix 2*, *Table 78*, and *Figures 38* and *39*). The incremental cost per additional participant to have an improvement of ≥ 9 points in SNOT-22 score was £4303, compared with £4855 at 12 months. The difference in the ICER was driven by the larger proportion of participants in the septoplasty arm experiencing an improvement of ≥ 9 points in SNOT-22 score at 6 months than at 12 months.

TABLE 16 Incremental cost per improvement in SNOT-22 score at 12 months

Investigation strategy	Cost (95% CI) (£)[a]	Incremental cost (95% CI) (£)[b]	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an improvement in SNOT-22 scores				
						£0	£500	£1000	£3000	£5000
Outcome: SNOT-22 score – results										
Medical management (costs, *n* = 155; outcomes, *n* = 125)	973 (810 to 1137)	1306 (1124 to 1489)	0.504 (0.42 to 0.59)	0.269 (0.16 to 0.38)	4855	1.00	1.00	1.00	1.00	0.45
Septoplasty (costs, *n* = 152; outcomes, *n* = 119)	2162 (2102 to 2222)		0.756 (0.68 to 0.83)			0.00	0.00	0.00	0.00	0.55

a Point estimates are based on the unadjusted analysis (costs, *n* = 307, effects, *n* = 244).
b Incremental estimates are based on the adjusted analysis (*n* = 243).

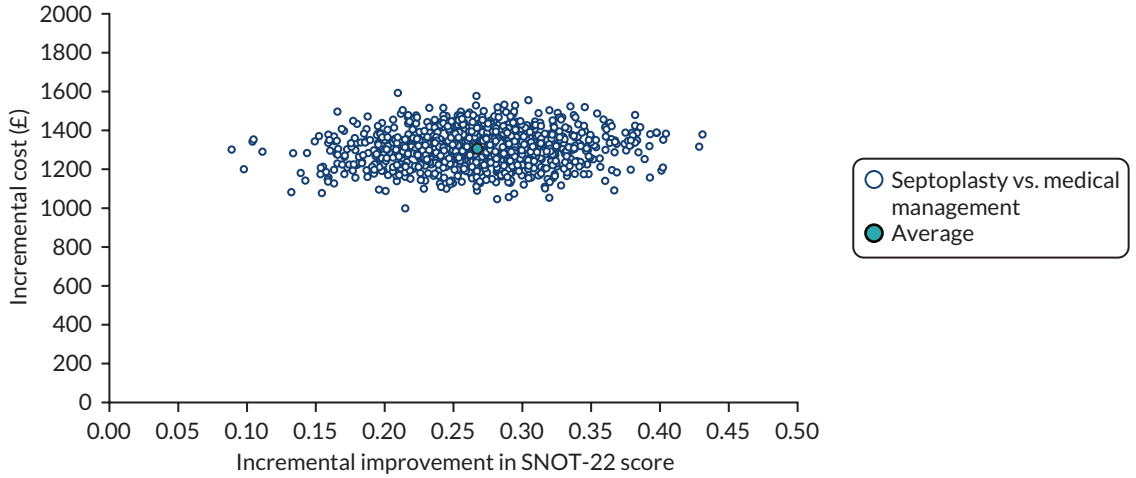

FIGURE 19 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CEA SNOT-22 score at 12 months (multiple imputation results).

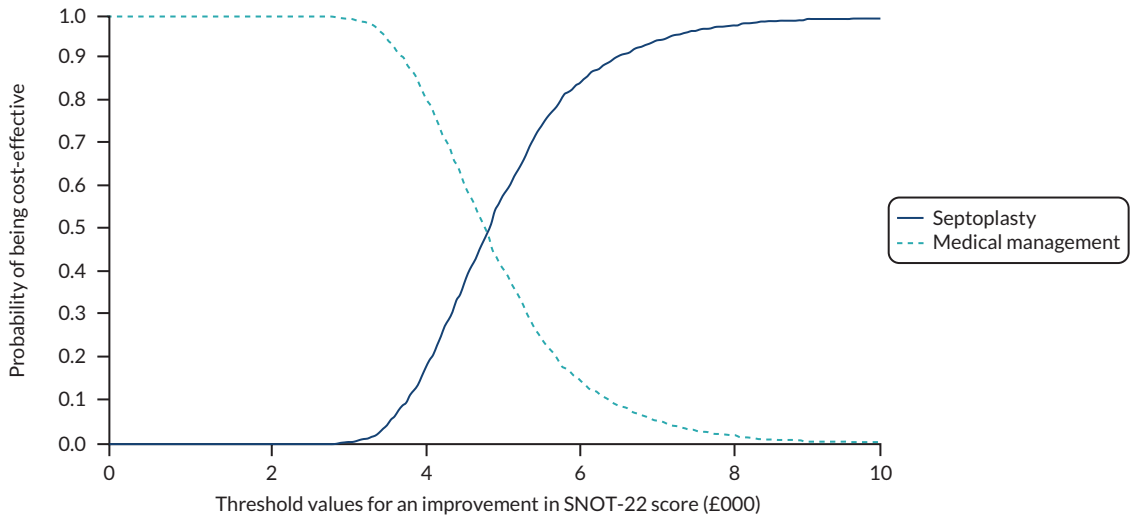

FIGURE 20 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CEA SNOT-22 score at 12 months (multiple imputation results).

The measure of effectiveness was the number of adverse events When the number of AEs was used as the measure of effectiveness in the CEA, septoplasty was, on average, more costly and less effective at reducing the number of AEs experienced by participants (see *Appendix 2*, *Table 79*, and *Figures 40* and *41*). In this analysis, septoplasty was dominated by medical management; over the range of threshold values considered to avoid an AE, the probability of septoplasty being considered cost-effective was zero.

Cost–utility sensitivity analyses

Surgery costs were estimated using microcosting and compared with the NHS tariff. When surgery costs were estimated using microcosting, the average total cost was £1276, which is lower than the NHS tariff of £1956. On average, septoplasty was more costly and more effective than medical management at 12 months (see *Appendix 2*, *Table 80*, and *Figures 42* and *43*), with an incremental cost per QALY of £16,682. The probability of septoplasty being considered cost-effective was 79% at a £20,000 threshold for an additional QALY.

TABLE 17 Incremental cost per QALY gained at 12 months

Investigation strategy	Cost[a] (95% CI) (£)	Incremental cost[b] (95% CI) (£)	Effect[a] (95% CI)	Incremental effect[b] (95% CI)	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an additional QALY				
						£0	£10,000	£20,000	£30,000	£50,000
Outcome: QALYs – results										
Medical management (costs, *n* = 155; outcomes, *n* = 152)	973 (810 to 1137)	1193 (1018 to 1368)	0.728 (0.71 to 0.75)	0.044 (0.03 to 0.06)	27,114	1.00	1.00	0.85	0.32	0.01
Septoplasty (costs, *n* = 152; outcomes, *n* = 149)	2162 (2102 to 2222)		0.767 (0.75 to 0.79)			0.00	0.00	0.15	0.68	0.99

a Point estimates are based on the unadjusted analysis (costs, *n* = 307; QALYs, *n* = 301).
b Incremental estimates are based on the adjusted analysis (*n* = 299).

Participant costs

When costs incurred by participants were included in the analysis, septoplasty was, on average, more costly and more effective at 12 months (see *Appendix 2*, *Table 81*, and *Figures 44* and *45*). The incremental cost per QALY was £24,136, and septoplasty had a 29% probability of being considered cost-effective at a £20,000 threshold.

Costs and quality-adjusted life-years were estimated for all participants with complete data only (i.e. no imputations for missing data)

When costs and QALYs were estimated for those with complete cost data (n = 204) and QALY data (n = 210), septoplasty was, on average, more costly and more effective at 12 months (see *Appendix 2*, *Table 82*, and *Figures 46* and *47*). The incremental cost per QALY was £37,371, and septoplasty had a 0% probability of being considered cost-effective at a £20,000 threshold, which increased to 23% and 83% at £30,000 and £50,000 thresholds, respectively.

The eligibility criteria were changed

When costs and QALYs were estimated for those who were classified as severe or extreme at baseline based on their NOSE scores (N = 267: medical management, n = 133; septoplasty, n = 134), septoplasty was, on average, more costly and more effective at 12 months (see *Appendix 2*, *Table 83*, and *Figures 48* and *49*). The incremental cost per QALY was £22,980, and septoplasty had a 24% probability of being considered cost-effective at a £20,000 threshold, which increased to 89% at a £30,000 threshold.

Incremental cost per quality-adjusted life-year at 6 months

When costs and QALYs were estimated at 6 months, septoplasty was, on average, more costly and more effective than medical management (see *Appendix 2*, *Table 84*, and *Figures 50* and *51*). The incremental cost per QALY was > £100,000, and septoplasty had a 0% probability of being cost-effective at the different threshold values for an additional QALY. This result is expected, as the shorter follow-up is effectively a bias against the more effective surgery because it allows for less time for gains in QALYs to offset the initial higher costs of surgery.

Model-based

Introduction

The within-trial results are useful to inform decisions about the cost-effectiveness of septoplasty in the short term (12 months). However, they provide limited information on the costs and benefits associated with septoplasty over the longer term. This is an important limitation of the within-trial analysis. We anticipated that the surgical arm could be more costly and potentially more effective, but the time horizon of the trial would not be sufficient for the additional benefit to offset the additional costs. This is illustrated in the analyses presented above when we compare the incremental cost per QALY for septoplasty versus medical management at 6 months' follow-up (>£100,000) with that at 12 months (£27,114). To address this, we conducted a further model-based analysis. The question being addressed by the model-based analysis was as follows:

> *For adults suffering with nasal obstruction associated with deviated septum, if costs and effects were extrapolated beyond the 12-month follow-up period, at what point, if any, does surgical management have the higher probability of being considered cost-effective compared with medical management?*

For the model-based analysis, the following outcomes are reported:

- NHS/PSS costs of managing individuals with nasal airway obstruction associated with a deviated septum (including septoplasty) over a longer time horizon
- QALYs over a longer time horizon
- incremental cost per QALY gained.

Methods

An economic model was used to extrapolate the trial findings and estimate the cost-effectiveness of septoplasty, compared with medical management, at 24 and 36 months post randomisation. The model design and parameters used are described in this section.

Economic model

Model structure

A simple decision tree model was developed using TreeAge (TreeAge Software, Inc., Williamstown, MA, USA) to extrapolate costs and QALYs beyond the 12-month trial follow-up period. The model was designed to replicate the pathway of the trial participants. *Figure 21* is an illustration of the model pathway. Data were obtained from the trial to estimate the relative costs and utilities of septoplasty, compared with medical management (see *Incremental cost–utility analysis*). Costs, QALYs and cost-effectiveness were estimated at 24 and 36 months.

Model assumptions

The model was designed to incorporate the relative differences between septoplasty and medical management identified from the within-trial analysis.

The following assumptions were made for the economic model:

- The model took the perspectives of the UK NHS and PSS.
- Costs and utility data used in the model were based on the multiple imputation data.
- Both arms of the model (medical management and septoplasty) were equivalent at the start of the model (i.e. it was assumed that costs and utilities reported by the medical management arm throughout the 12-month trial follow-up were the base for both arms).
- The utility and healthcare resource costs for those who went on to have surgery were assumed to be equivalent to the medical management arm plus an additional adjustment was made based on the trial data (see *Costs* and *Utilities* for further information).
- For extrapolation, the cost and utility values reported after 12 months were assumed to be the same as those reported in the last 6 months of the trial (i.e. between 6 and 12 months).
- Costs and utilities at 24 and 36 months were discounted at 3.5%.[113]
- Assumptions concerning further treatments (septoplasty and nasal sprays) post 12 months were based on clinical guidance and explored in sensitivity analyses.
- Given the short time horizon of the model, the average age of trial participants (40 years) and the trial data, it was assumed that no participants died over the 36-month time horizon.
- It was assumed, given the limited data available, that those who had surgery would not need a revision surgery.
- All model parameters were defined as statistical distributions in the model, and distributional assumptions were based on trial data.
- Alternative assumptions were explored in sensitivity analysis (see *Sensitivity analysis* below).

Model parameters

The model parameters were informed using trial data and the distribution of each parameter using the mean, SD and shape of the distribution. *Table 18* summarises all of the parameters used in the model.

Costs

The costs and cost adjustments for surgery used in the model are reported in *Table 18*. Intervention costs (surgery and/or nasal sprays) were assumed to be as reported in the trial and are assigned in the model depending on the pathway (i.e. nasal spray costs were assigned to the medical management arm only, the NHS tariff for septoplasty was assigned to those who went on to have surgery regardless of their randomised allocation). After 12 months it was assumed that there would be a demand for further treatments by those randomised to medical management. Those who went on to have surgery between 12 and 36 months were assigned the NHS tariff for septoplasty and those who continued with management received nasal spray costs for the remainder of the model.

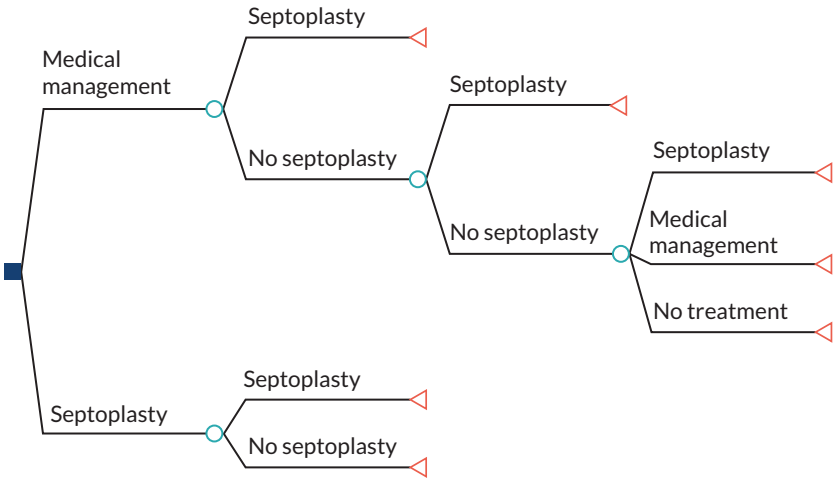

FIGURE 21 Model structure.

TABLE 18 Model parameters

Model parameters	Mean (SD)	Distribution
Costs		
Nasal spray	91 (–)	No assumptions made on distribution as this was a fixed cost
Surgery	1956 (–)	No assumptions made on distribution as this was a fixed cost
Healthcare resource use costs at 6 months (multiply imputed)	138 (235)	Gamma
Healthcare resource use costs at 12 months (multiply imputed)	148 (156)	Gamma
Healthcare resource use costs adjustment at 6 months for those in the septoplasty arm who had surgery	21 (23)	Gamma
Healthcare resource use costs adjustment at 12 months for those in the either arm who had surgery	−61 (18)	Gamma
Utilities		
Baseline	0.720 (0.14)	Beta
Utility at 6 months (multiply imputed)	0.728 (0.14)	Beta
Utility at 12 months (multiply imputed)	0.735 (0.15)	Beta
Utility adjustment at 6 months for those who had surgery in the septoplasty arm	0.063 (0.012)	Beta
Utility adjustment at 12 months for those in either arm who had surgery	0.068 (0.14)	Beta
Transition probabilities		
Probability of having surgery (medical management) at 12 months	0.30	No assumptions made on distribution as based on trial data
Probability of having surgery (medical management arm only) at 24 months	0.15	No assumptions made on distribution as based on clinical advice, but explored in sensitivity analyses

continued

TABLE 18 Model parameters (*continued*)

Model parameters	Mean (SD)	Distribution
Probability of having surgery (medical management arm only) at 36 months	0.075	No assumptions made on distribution as based on clinical advice, but explored in sensitivity analyses
Probability of having medical management at 24 and 36 months (medical management arm only)	0.50	No assumptions made on distribution as based on clinical advice, but explored in sensitivity analyses
Probability of having surgery (septoplasty arm only) at 12 months	0.97	No assumptions made on distribution as based on trial data

We assumed that healthcare resource use costs would be equivalent at the start of the model and adjustments were made depending on whether or not surgery had been performed. The adjustment in costs at 6 and 12 months was based on an ordinary least squares regression of the multiply imputed healthcare resource use costs at 6 and 12 months. The same covariates used in the SUR (randomised arm, age, gender, ethnicity and baseline utility scores) were used. At 6 months, those randomised to septoplasty reported slightly higher healthcare resource use costs, but at 12 months they reported lower costs than those in the medical management arm (see *Table 18*). We assumed that healthcare resource use costs incurred after 12 months, assigned at 6 monthly intervals, were equivalent to those reported during the last 6 months of the trial (i.e. 12-month costs). Adjustments to healthcare resource use costs associated with surgery were assigned depending on when during the 36 months surgery was performed.

All costs (treatment and healthcare resource use) incurred after 12 months were discounted at 3.5%.

Utilities

The utility values and utility adjustments used to estimate QALYs in the model are reported in *Table 19*. Similar to costs, the multiply imputed utility data reported by the medical management arm throughout the 12-month trial follow-up were assumed to be the base and adjustments were made if surgery was performed. Similar to the cost adjustments, utility adjustments were estimated using an ordinary least squares regression controlling for the same covariates as the SUR (randomised arm, age, gender, ethnicity and baseline utility scores). At both 6 and 12 months, those randomised to septoplasty reported higher utility values; this adjustment was applied to the QALY equation depending on when septoplasty was performed. Similar to costs, utilities were assigned at 6-monthly intervals (18, 24, 30 and 36 months) and those incurred post 12 months were discounted at 3.5%.

TABLE 19 Incremental cost per QALY gained at 24 and 36 months (model results)

Investigation strategy	Cost (£)	Incremental cost (£)	Effect	Incremental effect	ICER (£)	Probability that septoplasty is cost- effective for different threshold values for society's willingness to pay for an additional QALY				
						£0	£10,000	£20,000	£30,000	£50,000
Outcome: QALYs at 24 months – results										
Medical management	1483	833	1.46	0.06	13,221	1.0	0.97	0.01	0.00	0.00
Septoplasty	2316		1.53			0.0	0.03	0.99	1.00	1.00
Outcome: QALYs at 36 months – results										
Medical management	1785	703	2.20	0.10	7368	1.0	0.05	0.00	0.00	0.00
Septoplasty	2488		2.29			0.00	0.95	1.00	1.00	1.00

Transition probabilities

Transition probabilities in the model were based on the probability of those randomised to each arm undergoing septoplasty; these probabilities are detailed in *Table 18*. As expected, a higher proportion of those randomised to septoplasty than to medical management underwent surgery (97% vs. 30%, respectively). We assumed in the base-case analysis that no additional surgeries were undertaken at 24 or 36 months for those randomised to septoplasty. Based on clinical advice, we also assumed that there would be a steady decline in the uptake rate of septoplasty for those in the medical management arm after 12 months, and that a proportion of those randomised to medical management would recommence using nasal sprays to manage their deviated septum. These assumptions were explored in sensitivity analyses that varied the transition probabilities by ± 50%.

Model validation

We internally validated the model by checking the model structure, calculations and data parameters.[121] We undertook further validation of the model by running it for 12 months, to replicate the results of the within-trial analysis. Comparing these results allowed any potential discrepancies in the model parameters to be identified.

Sensitivity analysis

A probabilistic sensitivity analysis was undertaken to quantify any potential uncertainty in the model based on the model parameters. Each model parameter, except the intervention costs (surgery and nasal spray) and transition probabilities for surgery, which were fixed, had a measure of uncertainty surrounding it (SD) and was assigned a statistical distribution. The probabilistic sensitivity analysis facilitates the estimation of costs and effects using a set of parameters drawn from the statistical distribution using Monte Carlo simulations. Similarly to the bootstrapping of the within-trial results, 1000 Monte Carlo simulations were drawn to estimate the probability of septoplasty being considered cost-effective at a range of thresholds for an additional QALY.

Results

The model results at 24 and 36 months are presented in this section.

Costs

Similar to the within-trial results, septoplasty was, on average, more costly than medical management at both time horizons (24 and 36 months). *Table 19* details the average total costs for both arms at each time horizon.

Effectiveness

Septoplasty was, on average, more effective in terms of QALYs gained at 24 and 36 months (see *Table 19*).

Incremental cost per quality-adjusted life-year gained

Table 19 details the model results at 24 and 36 months. The conclusions of the model remained similar to that of the within-trial results in that septoplasty was, on average, more costly but more effective than medical management. However, as we extrapolated costs and QALYs over a longer period (36 months), the incremental cost per additional QALY reduced to £13,221 (at 24 months) and £7368 (at 36 months). At 24 and 36 months, septoplasty had the highest probability of being considered cost-effective at a £20,000 threshold for an additional QALY, compared with medical management (99% at 24 months, 100% at 36 months; see *Appendix 2*, *Figures 52–55*).

Sensitivity analyses exploring variations in the probability of surgery in the medical management arm did not change conclusions: septoplasty had the higher probability of being considered cost-effective at a £20,000 threshold for an additional QALY at 24 and 36 months.

Chapter 5 Qualitative research integrated within Trials Recruitment Intervention study

Introduction

Randomised evaluations of health care are vital to promoting an evidence-based culture in surgery, but executing them to a high standard can be challenging.

The NAIROS team anticipated challenges in recruitment, based on the members' own experiences of previous/ongoing surgical trials and awareness of the existing literature and others' experiences of under-recruitment. Engagement with patients and members of the public in designing the NAIROS also signalled the prospect of recruitment challenges, particularly patient and clinician preferences for surgery. We anticipated significant recruitment challenges in this RCT, particularly as we assumed that many patients would have been prescribed steroid sprays prior to hospital referral. The study team also foresaw the possibility of surgeons' habitual practices and individual experiences complicating recruitment.

Given these concerns, the NAIROS included an integrated QRI: a complex intervention that seeks to prevent and address recruitment issues in RCTs. Since conception of the QRI methods in the NIHR-funded Prostate cancer testing and Treatment (ProtecT) study,[122,123] the QRI has iteratively developed through its application to many RCTs deemed challenging for recruitment, culminating in publication of the QRI protocol in 2016,[124] and methodological guidance on how to implement the intervention.[125]

The ethos of the QRI is to develop an empirically grounded, rapid understanding of recruitment, and then use these insights to design tailored solutions to optimising recruitment. This occurs in two cyclical phases that run contemporaneously to the trial's recruitment period. Recruitment issues are investigated in phase 1; these inform which actions are required to optimise recruitment in phase 2.

The QRI was incorporated into the NAIROS trial partway through its competitive funding application, and thus the budget for this work was limited. The QRI was funded for 12 months of the 20-month recruitment period, to coincide with the planned internal pilot. A new 'pre-emptive' phase was also incorporated into the NAIROS, consisting of activities to optimise recruitment from the inception of the NAIROS (e.g. training). This stage drew on a wealth of evidence from previous RCTs that had integrated QRIs, and the latest published literature. When sites opened to recruitment, the pre-emptive phase was followed by the two-phased approach described previously.

Methods

The methods and activities spanning the pre-recruitment and recruitment phases of the NAIROS trial are outlined below.

Methods in the pre-recruitment phase: pre-emptive support

Anticipated sources of recruitment difficulty were addressed by:

- critically reviewing patient-facing materials
- designing and delivering training to raise awareness of common recruitment issues and solutions
- consolidating key messages from training in a written 'tips' document.

Methods in recruitment phase: phase 1 and phase 2 of the QuinteT Recruitment Intervention

Methods to investigate actual (rather than anticipated) recruitment processes in the NAIROS are outlined below (phase 1), followed by a summary of how these informed responsive actions to optimise recruitment (phase 2).

Phase 1 of the QuinteT Recruitment Intervention

Interviews with the Nasal AIRway Obstruction Study recruiters

Semistructured interviews were conducted with members of the TMG and with recruiting staff across sites, to explore views on the NAIROS question/study design and experiences of recruitment to date. The purpose of the QRI was explained in a 'healthcare professional PIS', and all interview participants gave written informed consent prior to the interview. Interviews were conducted over the telephone or face to face and were audio-recorded with permission. Interviews were guided by an interview schedule, informed by prior research and literature on recruitment to RCTs, including the QRI team members' experiences of working on previous RCTs. Topics covered included views about the NAIROS research question/design, organisation of recruitment processes at sites and experiences of inviting patients to consider trial participation.

Audio-recording of discussions between potential randomised controlled trial participants and recruitment staff

Recruiters across sites were encouraged to audio-record their appointments with potential RCT participants. Ten encrypted recorders were shared between 17 sites for the duration of recruitment. Both healthcare professionals and patients provided written informed consent for audio-recording appointments. Recordings were periodically securely transferred to the QRI team for analysis.

Screening log data collection and analysis

A log of each potentially eligible participant was created at site level and periodically sent to the NCTU, where the information was logged and maintained. This log was used to identify points where potential participants were lost from the recruitment pathway. We requested that sites complete the logs for all patients screened for trial participation who had a blocked nose and suspected deviated septum.

Analysis of phase 1 data

QuinteT Recruitment Intervention interviews were transcribed and analysed thematically using constant comparative approaches, adopted from grounded theory.[126] Transcripts were stored and managed using NVivo software, version 12 (QSR International, Warrington, UK) to facilitate analysis.

Audio-recorded recruitment consultations were transcribed selectively, focusing on discussion about the trial, with other parts of recordings summarised through notes. Consultations were analysed thematically, using inductive approaches, albeit with a priori interests informed by researchers' previous experience and engagement with the literature (e.g. communication of equipoise, elicitation and management of treatment preferences). Consultations were regularly revisited, often with a new analytical lens informed by other QRI activities and emerging recruitment issues. As a result, content analysis was sometimes employed when we intended to identify discussion pertaining to a specific topic. A detailed explanation of the blend of inductive and deductive approaches used for QRI consultation analysis have been reported elsewhere.[125]

The QRI analysis used several approaches to enhance rigour. Every transcript was independently coded by at least two researchers to enhance the credibility of the findings reported. Findings were discussed and refined through regular meetings between those involved in QRI data collection/analysis. We also intended to seek out 'negative cases' throughout, to ensure that the QRI findings were a full and accurate representation of the breadth of views/experiences (interviews) and practices (consultations) reported.

Phase 2 of the QuinteT Recruitment Intervention

The findings from phase 1 data sources were regularly shared with the TMG through reports and meetings, to inform the design and implementation of 'actions' to address recruitment issues. The actions implemented are described below in *Results*.

Results

QuinteT Recruitment Intervention activities are reported here chronologically, with empirical findings and actions to optimise recruitment reported in tandem across three sections:

1. pre-emptive strategies to optimise recruitment (i.e. before sites opened)
2. phase 1 QRI findings (understanding recruitment in practice)
3. phase 2 QRI actions to address sources of recruitment difficulty while the trial was under way.

Pre-emptive strategies to optimise recruitment

Given that the NAIROS team anticipated that patient preferences/expectations for surgery would be an obstacle to recruitment, key issues considered at the outset of the RCT centred around conveying equipoise and exploring treatment preferences, to ensure that patients were fully informed. These topics were covered in training materials and considered in patient-facing refinements to recruitment materials (e.g. PISs and videos), as summarised below.

Recruitment training

A trial launch meeting was held on 11 May 2017, prior to sites opening to recruitment. This included a recruitment training session covering the following elements:

- encouraging consistent messaging about the NAIROS within sites, among trial personnel and colleagues who may interact with patients along the clinical pathway; the training materials included short phrases that non-recruiting colleagues may use to avoid formulation (or reinforcement) of patient expectations for surgery (e.g. 'We do not know which treatment is better', 'You'll be hearing about the NAIROS study')
- suggested wording for introducing the NAIROS, to convey its national scale and integration with NHS care
- raising awareness of equipoise, including what the term means, and ways it can be lost in communication with patients
- encouraging recruiters to explore and understand patients' treatment preferences, with a view to safeguarding informed consent.

The points relating to communication were reinforced through a 'tips and guidance' document: a single sheet of bullet points to support recruiters' explanations of the trial. This was disseminated to all sites at the trial launch. The aforementioned pillars of recruitment training were carried forward to the site initiation visits held with each centre before they opened to recruitment.

Revisions to the participant information sheet

The PIS was scrutinised in terms of its clarity and consistency and how well it captured the equipoise underpinning the NAIROS. Revisions to the PIS were informed by previous research, including evidence around ways in which equipoise can be over-ridden or undermined,[127] patients' understanding of common explanations of randomisation[128] and insights from previous RCTs with integrated QRIs or qualitative process evaluations led by NAIROS team members. Iterations to the PIS were made over several reviews between April to November 2017.

Several statements throughout the original PIS (version 0.1) were identified to be potentially disruptive for conveying equipoise. For example, the nature of the clinical problem was often framed in terms of

the patient's deviated septum, rather than their symptoms of nasal obstruction. This was addressed through edits that framed the clinical problem around patients' symptoms of blocked nose, as per the trial protocol. In alignment with this, further revisions aimed to address any subtle indications that patients' nasal obstruction was definitely caused by the deviated septum. Statements were included to explain that nasal obstruction could be caused by inflammation and mucus (*Table 20*), and that people with septal deviations can experience normal breathing. The original PIS also focused on surgery a great deal, without equal mention to medical management. For example, the section on side effects covered only surgical risks, with no mention of the risks associated with medical management.

Other revisions to the PIS concerned the explanation of 'randomisation'. References to the computer 'deciding' treatment were removed and replaced with a description of the process and purpose of randomisation. This change was prompted by the process evaluation team's experience of working on a previous RCT, in which patients had assumed that the computer determined the best treatment for them. Findings from previous QRIs had also indicated that patients can interpret the computer as having agency.[128]

TABLE 20 Revisions to the PIS to improve the clarity and accuracy of information provision about the NAIROS

Key concepts/ issues	Details of issues	Changes implemented
Conveying equipoise	Presenting the twisted septum as the main problem requiring resolution: *Doctors do not know whether surgical care (septoplasty) or medical management is the best method for treating a twisted septum (midline nasal partition)* *PIS version 0.1*	Focus on the symptoms of the blocked nose, rather than the anatomical deformity (the deviated septum): *Doctors do not know whether surgery (septoplasty) or medical management is the best method for treating problems with a blocked nose (nasal airway obstruction)* *PIS version 0.7*
	You have been referred to the Ear, Nose and Throat clinic as you have had problems breathing through your nose due to a suspected twisted septum *PIS version 0.1*	*You have been referred to the Ear, Nose and Throat clinic as you have had problems breathing through your nose ('nasal airway obstruction')* *PIS version 0.7*
	Presenting the twisted septum as the cause of the nasal blockage: *You have had problems breathing through your nose due to a suspected twisted septum*	Presenting uncertainty about the cause and best treatment for the nasal blockage: *The nasal airway obstruction could be due to inflammation and mucus which affect breathing through the nose. A twisted septum can cause problems with breathing through the nose but it is not always the cause of nasal airway obstruction. Sometimes people with a very twisted septum can still breathe fine through their nose* *PIS version 0.7*
	Only risks of surgery presented under 'risks' and 'side effects'	Incorporation of two subsections: one covering risks of surgery and one covering risks of medical management
Explanation of trial terminology: 'randomisation'	References to a computer 'picking' a treatment: *Your group will be picked by a computer. We call this 'randomisation'. Your doctor will not have any say on which group you are put in* *Version 0.1*	Presenting a full explanation of the process and purpose of randomisation: *The group you are allocated to will be determined by chance, through a process called 'randomisation'. This process will help us to achieve two groups of patients that are similar in every respect, with exception to the treatment they receive. This will help us to fairly compare these treatments at the end of the study. Neither you nor your doctor can choose the group you are assigned to, but the team involved in your care are confident that either group will be suitable for you* *PIS version 0.7*

Feedback from the PPI panel review of the draft PIS was incorporated into the updated version of the PIS included in substantial amendment 1 to the REC. This was the first version of the PIS implemented at sites.

Refinements to recruitment video script

The aforementioned principles informed the content of a recruitment video which simulated a recruitment consultation between an ENT consultant and a potential participant (a patient actor). We reviewed the script several times to ensure it was consistent with the edited PIS and recruitment training materials. Script edits focused largely on conveying equipoise, as the details around medical management were less well developed in comparison with the details for septoplasty. Trial processes were also often described in terms of surgery, rather than medical management. In summary, the revisions were centred around:

- identifying areas of the script where surgery was described and explained without similar attention devoted to medical management
- increasing information about medical management (e.g. period of intended use).

Phase 1: QuinteT Recruitment Intervention findings – understanding recruitment in practice

The first site opened to recruitment 5 months later than planned, in January 2018, owing to governance and regulatory approval delays. Ten sites were projected to be open by this point. With recruitment already behind schedule, rapid understanding of barriers to patient accrual was critical in the remaining 7 months of the funded QRI.

All phase 1 QRI data collection (apart from two preliminary interviews with TMG members which were conducted before began) was focused on actual recruitment interactions and experiences. QRI data collection in phase 1 comprised 19 interviews, 108 audio-recorded consultations and regular scrutiny of screening logs. Findings from these sources were triangulated to build an in-depth understanding of recruitment processes across sites. Findings from the interviews and audio-recorded consultation analysis are presented separately, with cross-references to other data sources when relevant.

Screening log analysis over first 6 months

Scrutiny of monthly screening logs provoked questions about how recruitment was organised across the NAIROS sites. Logs collected over the first 6 months indicated that most eligible patients consented to randomisation, with many sites having 100% conversion rates. The number of patients entered on the logs was, however, highly variable, prompting questions around processes for identifying and approaching patients across sites. For example, no patients had been entered onto the log over the first 2–3 months of some sites opening to recruitment. The early stages of identifying/approaching patients became a key focus for further investigation in QRI interviews.

Interview findings

Sample of interview informants and presentation of findings

A total of 19 recruiters, from 11 of the 15 sites open to recruitment at the time, participated in interviews between May 2017 and August 2018. Of these 19 informants, three were research nurses and 16 were consultant ENT surgeons. Most informants (17/19) had experience of recruiting to the NAIROS as their sites had been open for 2–5 months at the time of interview. Two interviews were conducted before recruitment began with individuals who held dual roles as recruiters and TMG members. Thirteen of the 19 interviews were semistructured and directed by the QRI topic guide. Six were structured discussions about sites' recruitment pathways.

Findings from the interviews have been presented according to three topics: (1) perceptions of equipoise and the need for the NAIROS, (2) organisation of recruitment at the site level and (3) experiences of discussing the trial with patients. Illustrative anonymised quotations have been

presented throughout, with careful attention to present negative cases when relevant. Identifiers for quotations show the following:

- the interview participant's number ('R' = 'recruiter')
- site number, specific to the QRI study (note that a QRI-specific site numbering system was used that was different from the wider trial's site numbering; this was partly because only a subset of sites took part in the QRI study. The QRI-specific numbering system also preserves sites' anonymity)
- role of the individual [research nurse or surgeon, with an indication of which surgeons were also the principal investigator (PI) for the site].

Perceptions of equipoise and the need for the Nasal AIRway Obstruction Study

Recruiters' perceptions of equipoise were explored in the early stages of the QRI to provide context for understanding recruitment issues, but these were also important topics covered in the trial's qualitative process evaluation (see *Chapter 6*). To avoid replication, detailed insights around recruiters' perceptions of the trial question and eligibility criteria are reported in the context of the process evaluation, which builds on some of the data collected for the QRI. In terms of optimising recruitment, the below findings (relating to this part of the QRI topic guide) were key:

- Surgeons and research nurses indicated support and commitment to recruiting to the NAIROS, acknowledging a need for evidence to inform policy and practice around management of nasal obstruction. Several informants (all surgeons) alluded to the NAIROS's significance to commissioners and policy-makers, as shown through comments that there was an increasing expectation or 'demand' (R9, site 5) to produce evidence to justify continuation of existing practices:

  > *I think it's a really important subject. Politically, it's important [...], where there are increasing pressures to give good evidence that what we're doing, optimally, for patients is the right thing and is going to be a proven benefit for them.*
  >
  > *R15 (surgeon PI, site 7)*

- Most surgeons anticipated that the NAIROS would address clinical uncertainties around which patients would benefit the most from septoplasty. In alignment with this, most surgeons anticipated that the NAIROS would show a relationship between degree of septal deviation and benefit:

  > *I think it will show that, in patients who have significant symptoms, and a significantly deviated nasal septum, that there are benefits to be had from surgery. So I think it will be very much based on our baseline stratification.*
  >
  > *R11 (surgeon, site 6)*

- Most informants expressed that they were comfortable with and willing to approach the full spectrum of eligible patients for the NAIROS, despite some surgeons acknowledging that this required them to over-ride instincts about which patients would benefit from septoplasty. Two surgeons raised the prospect of not approaching patients whom they felt would benefit from a surgical procedure outside the NAIROS protocol. Based on interviews/screening log data, it was not possible to gauge the extent to which this quantitatively affected recruitment.

These findings provided insight into clinical professionals' vantage points as they embarked on recruiting to the NAIROS (see *Chapter 6* for more insights about eligibility assessment).

Organisation of recruitment at the site level

Recruiters' interview accounts revealed variable ways in which the NAIROS had been integrated within routine practice, which had potential to support or hinder recruitment, specifically by having implications for the identification of potentially eligible patients (referred to as 'NAIROS candidates' hereafter).

Identifying Nasal AIRway Obstruction Study candidates and ascertaining eligibility Initially, most (and eventually all) sites relied on dedicated research clinics, to conduct eligibility assessments, consent discussions, randomisation and baseline assessments, given the difficulties of incorporating these tasks into time-limited routine clinics:

> *The first time we did it, it took us 2 and a half hours, and that is purely because it was the first time we were doing it. You need to cater for the patients needing to go through all that. So, it's not really feasible in a clinic setting.*
>
> *R20 (surgeon PI, site 10)*

Most sites were able to accommodate research clinics into clinical schedules, but their frequency varied, ranging from once a week to once a month. Therefore, although NAIROS clinics were necessary, their frequency and the limited numbers of patients they could accommodate constrained recruitment:

> *... our clinics are full every month. We don't have scope at the moment to add more patients in [...], room space is a problem. We have a room and the consultant has a room, so if we're both recruiting different patients, even if we stagger patients, we would still need an extra room.*
>
> *RN7 (research nurse, site 3)*

Although most sites had managed to set up research clinics, identifying patients to invite to these clinics was a commonly reported challenge across sites. Research nurses and surgeons described two approaches to identifying NAIROS candidates, as shown in *Figure 22*.

The first method involved screening referral letters accessed through 'choose and book' (described below) and written referral letters. Site PIs (all of whom were surgeon consultants) tended to triage patients referred to their own clinics, with further involvement from research nurses and other consultants depending on the site. Irrespective of who and how many individuals were involved in screening, identifying patients based on referral letters alone had its limitations. According to several recruiters, letters did not contain the level of detail needed to gauge NAIROS suitability, resulting in those screening erring towards a more inclusive approach. As a result, the limited capacity research clinics could be filled with patients who were not even suitable for eligibility testing:

> *We've found it quite difficult, I think, to assess patients adequately enough from the GP letters, so it's difficult to know whether they're even a suitable patient until you bring them into the NAIROS [clinic]. For example, the first patient that I saw in the clinic had other problems with their nose that meant that they were ineligible to meet the eligibility criteria.*
>
> *R15 (surgeon PI, site 7)*

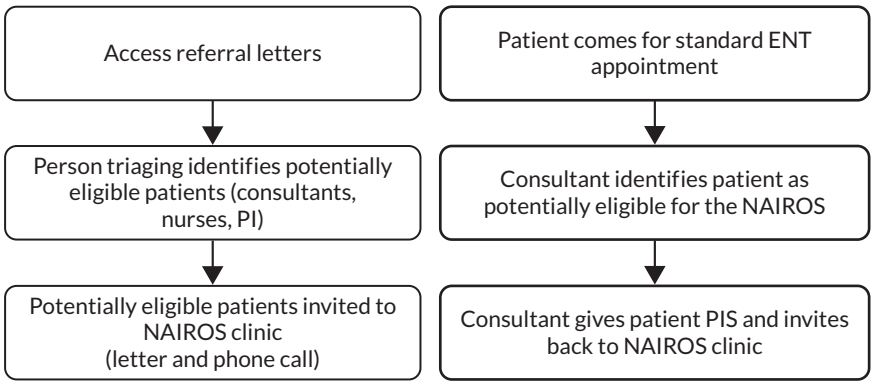

FIGURE 22 Approaches to identifying patients potentially eligible for the NAIROS from routine NHS care.

Some sites were able to address these issues with support from research nurses, who were able to conduct additional investigations of patient records to better gauge suitability, but this support was not universally available.

Another limitation of identification through letters was the transition to electronic 'choose and book' processes in some sites, whereby patients select their own appointment in routine clinics. Informants from one site explained that as a result of these 'choose and book' proceses, patients had often already arranged their routine care appointment when they were invited to attend a NAIROS clinic:

> *Patients, when they get their information pack, are usually halfway along the journey.*
>
> *R1 (surgeon PI, site 1)*

Considering the above difficulties, most sites either moved towards relying on consultants to identify patients who had been referred to their routine clinics (see the pathway on the right in *Figure 22*), or reportedly adopted this approach from the outset. According to several informants, consultant-led identification in clinics had the benefit of greater precision in referring suitable candidates to NAIROS clinics:

> *... if we draw our patients from a pool that have already been already seen in the main clinics and are already deemed as potentially suitable for septal surgery or a trial of medical treatment, I think that's probably the way forward. Otherwise, I think you end up spending a lot of time seeing patients that, probably, will never have been eligible to be included in the trial in the first place.*
>
> *R15 (surgeon PI, site 7)*

'In-clinic' identification was operationalised in different ways across sites, with each model involving consultants who did not hold formal recruitment roles. In some sites, consultants examined patients in routine clinics and referred potentially eligible candidates to research clinics. In others, consultants triaged letters and re-routed patients with a septal deviation to a research nurse or the routine clinic of the NAIROS PI, who would then invite suitable candidates to research clinics:

> *I'm the main recruiting clinician. [...] We triage our inpatients every week. So different consultants would triage patients and then they will identify potential patients who might fit the NAIROS criteria and let me know about them.*
>
> *R9 (surgeon PI, site 5)*

The success of in-person identification of NAIROS candidates hinged on engagement from clinical staff who were not directly involved in the NAIROS. Informants varied in their impressions of how engaged their colleagues had been, but several emphasised the importance of regular promotion of the NAIROS, through presentations and departmental meetings:

> *Because I think the thing about recruitment, you've got to remind people all the time, yes? Putting just a poster is not enough. [...] Yes, so I'm seeing them – I think it's the [date] is our [meeting name] – and I will remind everybody. That's the whole department there, which is good. So all the consultants, all the registrars, all the doctors.*
>
> *R18 (surgeon PI, site 9)*

Supporting non-Nasal AIRway Obstruction Study consultants to introduce the trial There was some indication from interviews that recruitment to the NAIROS was being constrained by patients declining invitations to attend research clinics:

> *So, for every one that considers it, I think there are at least two who would say, 'No, no'. So, round about 40–50%. It is high.*
>
> *R20 (surgeon PI, site 10)*

The original NAIROS screening log did not capture events preceding eligibility assessments, and thus the proportion of patients lost in the pathway before hearing the 'full explanation' of the trial was not formally documented. Interviews did, however, highlight the ENT consultants' pivotal role in introducing the trial, in addition to their role in identifying candidates:

> *... well, usually it's not easy to find someone that is a proper candidate for the study, for different reasons. But even when you do that, sometimes it's not easy seeing the patient in 15 minutes of an appointment to easily introduce them to the study or to have enough time to do that. I believe this is not only for me, it's for everyone, because we try to ask the help of other clinics so we can get someone that is a candidate. I mean, it doesn't need to be too long or too much to introduce the patient at the start, but sometimes it's not easy to get there.*
>
> *R19 (surgeon, site 9)*

Taken together, these accounts reinforced the idea that NAIROS recruitment relied on events and processes that preceded the formal 'recruitment setting' outlined in the protocol. Engagement from non-recruiting clinicians in identifying patients and providing high-level introductions to the trial appeared to be key to recruitment success.

Recruiters' experiences of discussing the trial with patients

Explaining the NAIROS to patients was a key element of the recruitment process. The sections that follow are based on recruiters' interview accounts, and draw on their experiences of explaining the trial.

Informants from sites that had not yet opened to recruitment anticipated that patient expectations and preferences for surgery would be a key barrier to recruitment. Those with recruitment experience (at the time of interview) also reflected back on their belief that patients would expect or prefer septoplasty. This belief stemmed from their assumption that many patients would have already received steroid sprays in primary care:

> *I think the majority will probably come, or the majority who have a preference will have a preference towards surgery. I think that's possibly culturally, and traditionally, because in the UK, unlike a lot of other healthcare systems, you have a general practice where you have a sort of gatekeeping role. So, you have quite a lot of treatment done in general practice, and they will have had treatment in general practice, and so I think quite a few of them will, when you are referred to hospital, sometimes it's almost with an expectation you're going to have an operation.*
>
> *R11 (surgeon, site 6)*

Recruiters' descriptions of their actual patient encounters suggested that the above concerns had not materialised. Surgeons and research nurses from different sites commented that recruitment had proceeded better than anticipated, as evident through unprompted remarks about how patients' reactions had surprised them:

> *Yes, I think we are meeting our targets so far. I'm certainly surprised. I thought some patients would say no, but I think just about every patient we've approached has said yes so far.*
>
> *R4 (surgeon PI, site 2)*

In contrast to concerns about patients holding strong preferences/expectations for surgery, several recruiters discussed how the uncertainty around surgery versus medical management had resonated with patients:

> *I feel confident and there are some patients I've come across who genuinely don't know which way they would like to go – either medical therapy or surgical therapy – and they've been delighted that that's been taken out of their hand with the trial.*
>
> *R9 (surgeon PI, site 5)*

> *Certainly the feedback and the impression I'm getting from the patients we talk to, unless they've already definitely made up their minds which they want to try, which we've had a couple of … otherwise they seem quite open to it, the question itself, you know? A lot of them are maybe asking themselves, 'What is best? Should I take medication or should I have surgery?'.*
>
> *R6 (research nurse, site 3)*

Preferences were, nonetheless, still raised by several recruiters when asked about the main barriers to recruitment. When discussed, references to preferences were either tempered with the positive accounts of recruitment (as per the previous quotation from R6), or framed as a reason why some patients had declined participation:

> Interviewer: *From your perspective, what were the facilitators and the barriers to getting people engaged in the study?*
>
> R14 (Research nurse, site 6): *I think it is people who are determined that they want surgery. That's the biggest barrier. I think there has been three or four who quite clearly, from the outset, they maybe have reasonable reasons and rationale for wanting surgery. Again, that is something that, just through the way it's gone, has changed my mind. I thought NAIROS would struggle to recruit [...]. I thought that people would, once they got as far as this, would be expecting surgery and they would reject the ideas of the sprays because they would have tried that. So I thought it would be quite difficult to recruit to, but just from our first few clinics and first few patients, I can see that the questions for patients are much wider and they're not as straightforward.*

We may not have regarded preferences as a significant obstacle to recruitment as most recruiters expressed confidence in engaging with patients' preferences. There were some exceptions to this (n = 3, all research nurses), whereby informants framed preferences as a clear-cut signal to stop discussing the trial, as further discussion would be futile or inappropriate. Notably, two of these individuals had not been involved in the NAIROS from its outset and had not attended the pre-recruitment training. By contrast, all surgeons (including site PIs) indicated that they were comfortable exploring preferences, particularly if these appeared to be based on expectations for surgery:

> R1 (surgeon, site 1): *Most of them come with an expectation to have surgery.*
>
> Interviewer: *How do you manage that?*
>
> R1 (surgeon, site 1): *I tell them what the evidence is and why we conduct trials – to help decide what the best way to manage patients with this is. I help them to understand that if it's an anatomical obstruction, where the nasal septum is slightly off to one side and causing an obstruction that, actually, will have been there for most of their lives, but often their symptoms are only recent and so it's something else that's changed. That's where equipoise comes in, in that it's a good research question.*

The one informant who framed preferences as a dominant issue discussed this in the context of inviting patients to attend research clinics. This informant estimated that around half of patients had declined the invitation [see the quotation from R20 (surgeon PI, site 10) in *Supporting non-Nasal AIRway Obstruction Study consultants to introduce the trial*]; however, none of the other informants discussed these challenges.

In summary, interviews with the NAIROS staff provided an opportunity for staff to reflect on their interactions with patients. This was, for most, a positive experience. Nonetheless, these positive accounts must be considered alongside the fact that discussions in the research clinic are unlikely to reflect the views of those patients less willing to consider participating in the NAIROS. There is also a limit as to what can be confidently gauged from people's accounts of their interactions with others, especially when reflecting on past events. However, it was clear that many recruiters were surprised

about how patients had engaged with the trial, despite the existence of preferences and expectations for surgery. It was also clear that most recruiters felt equipped to engage with preferences and expectations. The final section presents findings from the analysis of audio-recorded recruitment conversations, to provide insight into how the trial was conveyed by recruiters and received by patients.

Analysis of audio-recorded consultations

Recruiters had already received multiple forms of training and resources to support communication when recruitment began, although these materials were based on previous QRI insights adapted for the NAIROS. Audio-recording NAIROS consultations provided opportunities for more specific feedback and training, based on the actual (rather than anticipated) issues to emerge.

Sample of consultations and presentation of findings

A total of 108 consultations with 105 patients were audio-recorded, contributed by 16 recruiters from eight sites. Of these:

- 15 consultations did not include any discussion about the NAIROS or treatment within/outside the trial
- the 93 remaining consultations included at least some discussion pertaining to the NAIROS.

Despite the pre-emptive recruitment training/resources, we labelled the consultations as 'pre feedback' or 'post feedback', depending on when recruiters first received NAIROS-specific feedback relating to their practices, either on an individual or on a group basis. For most recruiters, the first substantive feedback event occurred on 20 September 2018 (month 9 of the recruitment period). Two recruiters received individual feedback before this point (months 7 and 8 of recruitment). Of the 93 consultations, 57 were pre feedback and 36 were post feedback.

Most audio-recorded consultations were with patients who appeared to agree to randomisation, although the recruitment outcomes of consultations were not always captured, and recordings did not always align with screening log information. The outcome of the consultation was not a core focus when analysing the recordings; rather, the focus was on the clarity and accuracy of information provision and patients' reactions to information.

The key findings from the audio-recordings that informed feedback to recruiters are summarised in the following sections, *Conveying equipoise* and *Understanding patients' expectations and preferences*.

Findings are supported by illustrative extracts, labelled according to recruiter number ('Rx'), site number and consultation number. The speaker is represented as 'Rx' (recruiter) or 'P' (patient). All recruiters were surgeons, unless otherwise specified.

Conveying equipoise

Each of the 93 recordings included examples of recruiters articulating equipoise, using a variety of techniques to express and reinforce its meaning.

Some approaches to conveying equipoise aligned with the pre-emptive training and 'tips and guidance' documents issued in the 'pre-recruitment' phase. For example, the guidance suggested conveying equipoise by expressing:

- uncertainty around whether septoplasty or medical management was more effective for symptoms of blocked nose
- the appropriateness of both treatments for the eligible patient
- the advantages/disadvantages and practical/clinical considerations of both treatments.

These techniques were demonstrated in some form by all recruiters who contributed recordings. Uncertainty as to which treatment was best was most consistently articulated:

> *The idea of the study, as I said at the start, was that we're not entirely sure. In fact, we're not sure at all which type of treatment is better: whether surgery or having the spray in your nose improves things and whether one is working better than the other.*
>
> *R17, site 8, consultation 2*

Many recruiters routinely communicated that both treatments were standard, appropriate approaches to treating a blocked nose outside the context of the trial:

> *They're all good options. We don't know what the best option is.*
>
> *R10 (site 6, consultation 4)*

> *We could, quite happily, give you either treatment and both would be perfectly acceptable treatments.*
>
> *R17 (site 8, consultation 1)*

The 'tips and guidance' document was less prescriptive in terms of how to balance the treatment arms. It did not articulate any specific information about what advantages/disadvantages to mention. In practice, the recordings showed that descriptions of the trial arms' risks/benefits and practical considerations varied across recruiters, in terms of the type of information covered and the level of detail expressed. However, given the protracted nature of the recruitment and treatment pathway in the NAIROS, there is a possibility that recruiters provided further information about the risks/side effects of surgery before or after the recorded consultations provided. Some of the challenges relating to imbalanced explanations of the trial arms, as apparent through the recorded consultations, are integrated throughout the consultation findings presented below.

Uncertainty around surgery effectiveness In departure from the 'tips and guidance' document, some recruiters tended to specifically frame uncertainty around septoplasty, pointing out its lack of an evidence base and the possibility that it may not resolve nasal congestion. This approach was evident in many consultations where patients engaged with the premise of the trial and consented to randomisation, but there were also examples where this created a challenging foundation for recruitment. The prospect that surgery may not work was not a convincing rationale for randomisation to some, particularly those who had tried medical therapy before. For example, the prospect of surgery not working was not a sufficient deterrent for the patient below, who felt they should at least try it:

> *I don't think the spray's going to do anything to be honest, I don't. I honestly don't think it will work, so I'll just go straight for the operation [...]. Just go straight for the operation. If the operation's not successful, so be it.*
>
> *Patient, R10, site 6, consultation 1*

For this patient, medical management was not a viable option, as shown through their implicit assumption that it would not 'do anything'. This was based on their prior experience of spray use. In this patient's case, simply hearing that surgery may not work was insufficient to discourage them from trying it. In contrast to this extract, other consultations were foregrounded with uncertainty around whether surgery or medical management was more appropriate for addressing nasal congestion, with explicit mention of how medical management may successfully resolve symptoms. Many recruiters substantiated these points by explaining that the treatment in the trial would likely differ to what they had used before, which appeared to be an effective strategy for presenting medical management as a viable option:

> Patient: *I would have the operation because when I was in [place] they gave us that, the spray stuff and it's, it didn't seem to do much.*

R11, site 6, consultation 2: *Yes, do you remember which one it was that you had?*

Patient: *I can't remember. I had it for about … what? The spray, I used that for about 7, 8 months or something, but it didn't seem to do much.*

R11, site 6, consultation 2: *Yes, OK. The spray that we're using is a different one, more than likely. It may have been something like Beconase [GlaxoSmithKline plc, Brentford, UK]. In general practice it's usually (Beconase). We're using a newer generation one and we're using it in combination with a nasal salt spray and it's given to you as a package.*

Septal deviation and surgical mechanisms of action Some recruiters tended to frame the NAIROS discussion around the deviated septum and/or septoplasty's aim to straighten this anatomical deformity. Both recruiters and patients often directly or indirectly associated this with resolution of nasal obstruction. There were several examples of patients expressing a desire for their septum to be 'fixed' or 'go back to normal':

R12, site 6, consultation 1: *You've been asked to see us because you've got a bent partition to your nose. One of the treatments for that would be a surgical operation to try and straighten the partition of your nose.*

[Later]

Patient: *To be honest, I'd like to have it rectified and fixed and maybe having it straightened might be the best outcome …*

R17, site 8, consultation 5: *The point with all of this is clearly you've got a problem with a blocked nose that you're concerned about. We've had a look in and we've seen that the dividing partition of your nose – what we call the septum – is bent over to one side.*

Patient: *Yes. I just want to go back to normal.*

R17, site 8, consultation 5: *The problem that we've got is that there isn't any good evidence to show that, that being bent over, doing a procedure to straighten it up actually improves the breathing overall.*

Patient: *It definitely will.*

R17, site 8, consultation 5: *The assumption is that, 'Yes, it does', and that's why we've been doing the operation for years, but it doesn't work in everyone. In some people we look in, they've got a bent nose internally. The septum's bent over. They've got a blocked-up nose. We do an operation to straighten up and they say, 'You know what? There's no damn difference whatsoever. I'm still feeling completely blocked up.' Despite us looking in their nose and thinking, 'Well everything's straight'. What this study is aiming to do is to look at that situation and say, 'Actually, can we predict which patients will benefit from the surgery and which ones are going to be in that group that it makes no difference to?'*

Patient: *I'll definitely benefit, because I do a lot of physical exercise. That's where the big problem is.*

As illustrated above, surgery's potential to fix the bent septum resonated with some patients. Several recruiters adopted techniques that addressed this issue, including disassociating nasal obstruction from the septal deviation, and clarifying the spray's intended mode of action.

The following example was used to dissociate symptoms from deviation:

> *What we do know is that there are plenty of patients around who have a blocked nose and a straight dividing partition. The problem is more to do with the lining of their nose than it is to do with the shape of it. Clearly, we're trying to work out, 'How important are these two different aspects?'*
>
> *R17, site 8, consultation 5*

In a later example, the mechanism of action of spray was outlined:

> *Whether you have an operation to straighten your nose up or whether we give you some spray as a steroid to try and shrink the lining of your nose down a little bit and settle down any inflammation.*
>
> *R17, site 8, consultation 5*

'Delayed' surgery Some consultations included references to patients having surgery at the end of the trial if their symptoms had not resolved through medical management. Some patients appeared reassured by this, although there were also examples where these discussions overshadowed the notion of equipoise, as patients appeared to fixate on the timing of when they would receive surgery. In these examples, the discussion about the trial was dominated by the question of 'when' surgery would be performed, rather than surgery's comparative effectiveness relative to medical management:

> *It's still the 6 months with the steroid, nasal sprays and then possibly running to 12 months before the option of surgery? What I have right now, it's not hugely debilitating but it's a right nuisance. Another year, against 2, 4 months, I don't know, 6, I'm not sure, yes. Let's say I was part of the randomised group that was going to have the septoplasty, when would that happen?*
>
> *Patient, R11, site 6, consultation 1*

Understanding patients' expectations and preferences

Patient preferences featured regularly in the audio-recorded consultations, but did not arise as a major barrier to recruitment.

Preferences manifested on a spectrum, ranging from no preferred treatment, to clear-cut preferences for an arm and refusal of trial participation. Between these extremes, there were many examples where patients expressed concerns or views about treatments, which were subsequently explored and discussed. Only 8 out of 93 consultations included a clear articulation of a preference that precluded trial entry; 7 out of 8 of these were from 'pre-feedback' consultations. The remaining 85 consultations either did not include evidence of patients holding preferences (n = 53), or included patient views/concerns/preferences that shifted through exploration and discussion (n = 32).

The infrequency of articulated preferences may have been linked to recruiters' practices of conveying equipoise (discussed in *Conveying equipoise*), and/or may have reflected an already filtered sample of patients at research clinics. Nonetheless, consultation recordings included clear evidence of recruiters eliciting and exploring patients' treatment concerns and preferences, as suggested in the pre-recruitment training/guidance document.

On discussing their preferences or treatment concerns, most patients confirmed that they were happy to be randomised to either treatment, or explained their preference was not strong enough to deter them from trial participation (R8). Preferences for both surgery and medical management decreased following recruiters' provision of further treatment information (e.g. R17 and R12):

> R21, site 11, consultation 6: *OK, what about preferences at the moment? Having heard this, do you feel you would prefer one or the other or you don't know at the moment and that's why you're in the trial and this?*

Patient: *I don't know. I don't know which one would be more beneficial.*

Fine, yeah. I mean, naturally I'd prefer to go down the medical route, but I'm not going to rule one out because ultimately I just want it to be better than it is.

Patient, R8, site 4, consultation 2

R17, site 8, consultation 2: *Do you feel particularly that you want to do one treatment more than another?*

Patient: *I would have said the operation because I would think the operation would sort it. I think that's why I'm interested in doing this [NAIROS] because, as you say, it doesn't mean that it does solve the problem.*

Doctor: *When you say you would have – are you still feeling that you would prefer the operation now, or are you–?*

Patient: *I must admit I'm not that fussed really. […] I must admit I'm not that fussed at all. I would have taken it for granted that you would probably have known which was the best.*

R12, site 6, consultation 3: *So for you to enter the trial you'd have to be content with the idea of being listed for surgery, and if you're not content with that then the operation is not for you […].*

Patient: *Yes. It's not to say that I wouldn't be happy with, even, the operation if it looks like it's the right procedure to go down. It's just the matter of timing for me, like I was saying before, work commitments and whatnot. So that was probably. How long was the recovery?*

[Surgeon discusses recovery time]

Patient: *Well if that's the case I'm happy to … If it is a shorter space of recovery than I anticipated it might be, then that was the big stumbling block for me, to be honest.*

Eight of the consultations were with patients who appeared to decline trial participation on the basis of a preference. In one of these cases, the patient felt that they had not persevered with steroid sprays long enough, having heard the recruiter's explanation of the importance of persevering and complying with steroid sprays:

Patient: *I just don't feel as if I've used the sprays for long periods of time. I've maybe used them for a few weeks and then stopped. Nobody has said, 'Well, take them for longer'.*

R17, S8, consultation 3: *I think the reason that we – most patients if they've used them for about 6 weeks or so will be able to say whether they've got benefit from them. If you have only used it for a week or 2 then I'd say yes, probably you haven't given it long enough.*

In all other cases, patients had preferences for septoplasty, having tried sprays to no avail. In most cases, these appeared to be informed decisions, following recruiters' exploration of the type of sprays used, and information provision about the sprays used in the trial. There were, however, some examples where recruiters accepted patients' decisions without further discussion. In these cases, it was not clear if patients' views could have changed, as per other patients whose preferences dissolved on receiving further information.

Summary of recruiters' communication practices

Recruiters across sites were generally successful in implementing the QRI 'tips and guidance' issued at the start of the trial; this was evident from their generally clear articulation of equipoise and willingness to actively elicit and engage with patient preferences. Recordings did, however, identify new issues that

undermined equipoise, such as foregrounding consultations with discussion about the septal deviation, and failure to explain the intended mechanisms of action for both surgical and medical management arms. There were also some examples of recruiters accepting preferences at face value, without further exploration.

In addition to highlighting potential sources of recruitment difficulty, the consultations also provided insight into examples of successful techniques for addressing the above issues, providing an ideal source for feedback and training. The final section summarises how these insights, alongside findings from interviews, were formulated into phase 2, 'QRI actions', to support recruitment throughout the remainder of the NAIROS.

Phase 2: actions to optimise recruitment

The findings from the interviews and audio-recorded consultations were initially fed back to the chief investigator via a report in August 2018 (month 8 of recruitment) and circulated to the TMG in September 2018. The report informed a series of actions which are summarised in the following sections.

September 2018: investigators' meeting

Principal investigators, research nurses and consultants from all 17 sites were invited to an investigators' meeting held on 20 September 2018. Sites that were not yet open to recruitment were also invited to attend. The meeting slides and recording of the presentations were broadcast via a live link to individuals who could not attend and recorded and disseminated to all sites for retrospective viewing. The QRI feedback slides focused on two core topics identified as priority areas for optimising recruitment: strategies for identifying eligible NAIROS participants from routine clinics and explaining the trial to patients.

Key lessons captured in the feedback highlighted the challenges of identifying patients through referral letters, as well as the importance of engaging clinical colleagues to support 'in-clinic' identification of NAIROS candidates. Communication feedback drew on anonymised extracts of recorded consultations to illustrate 'good practice' and issues to avoid, and focused primarily on:

- providing recruiters with NAIROS-specific strategies for conveying equipoise – specifically, the importance of framing the medical problem around symptoms of blocked nose rather than septal deviation and explaining the ways in which medical management could plausibly help to address symptoms of blocked nose
- caution around placing too much emphasis on the prospect of receiving surgery at the end of the trial if medical management had not worked, in the light of audio-recordings revealing how this could overshadow the uncertainty around the comparative effectiveness of medical management versus septoplasty
- examples of how to address patient preferences – specifically when patients attended recruitment consultations having already tried medical management.

September 2018: updated 'tips and guidance' document

The QRI team, the chief investigator and the TMG collaboratively produced an updated 'tips and guidance' document for recruiters, informed by the evidence from the phase 1 report shared with the TMG. The document featured more bespoke strategies for explaining the NAIROS, informed by findings from the audio-recorded consultations. This was disseminated to all sites at the September 2018 investigators' meeting, and issued to sites via e-mail. It was also provided to sites at subsequent site initiation visits for new sites that opened after the investigators' meeting.

Consultant 'cue card' and video, to support non-recruiting ear, nose and throat consultants to introduce the Nasal AIRway Obstruction Study

Phase 1 findings indicated that the key obstacle to recruitment to the NAIROS was the identification and referral of patients to NAIROS clinics or NAIROS recruiters. Engagement with ENT consultants who were not directly involved in the NAIROS emerged as an important priority in efforts to optimise

recruitment, and thus efforts were focused on supporting PIs to achieve this locally. Interviews had provided insight into the challenges of providing a high-level, comprehensive introduction to the trial in routine NHS clinics. In response to this, the QRI team and the TMG produced a single-page 'cue card', comprising a series of bullet points to support non-recruiting consultants to introduce the trial. The cue card was reinforced through a simulated video of the chief investigator articulating the points to a patient actor. The video and cue cards were disseminated to sites on 1 December 2018.

Site-specific teleconferences to address identification/approach issues

The QRI researchers, the chief investigator and the trial manager organised and conducted a series of recruitment teleconferences with sites identified to have lower than anticipated screening activities, as indicated through continued scrutiny of monthly screening logs after the investigators' meeting. The teleconferences focused on local organisational and logistical issues, to increase the absolute numbers of NAIROS candidates identified/approached. The teleconferences were conducted at five sites between 10 December 2018 and 7 February 2019, with site PIs and research nurses. All those who attended these teleconferences were encouraged to use the resources developed (i.e. cue cards and video).

Equipoise/preferences remote training webinar

A dedicated training webinar focusing on recruitment communication – specifically, conveying equipoise and engagement with patients' treatment preferences – was arranged in the later stages of the trial to support recruiting and non-recruiting ENT surgeons to manage patients' expectations/preferences for surgery. Drawing on insights and examples of 'good practice' from the audio-recorded consultations, the QRI team, the chief investigator and clinical members of the TMG produced a script/video of a recruitment encounter illustrating examples of how to respond to patients' expectations/preferences. This was coupled with a training presentation, delivered live to NAIROS sites in September 2019. Copies of the recordings/slides were shared with all sites following the webinar.

Nasal AIRway Obstruction Study recruitment outcomes

Overall, despite anticipated challenges, the NAIROS successfully recruited its target sample without the need for a funding extension. Although there were substantial delays in sites opening and a change to the original planned pilot time frames, the intended sample size was achieved within 22 months, 1 additional month relative to the anticipated recruitment duration. Participants were recruited from each of the 17 sites that opened to the NAIROS, with no site closures. Recruitment issues were identified as the trial progressed, but it was possible to address these through tailored actions. This chapter has outlined plausible ways in which the QRI supported recruitment, through pre-emptive and responsive actions.

Limitations of the QuinteT Recruitment Intervention

Although it was possible to discern key recruitment issues and deploy strategies to address these through the QRI, there were limitations around the reach and depth of the methods. The sample of recruiters who agreed to audio-record consultations and participate in an interview were self-selected, and not all recruiters/centres took part. Therefore, a full picture of recruitment across all sites was not possible, potentially hindering opportunities for further bespoke recruitment support. The QRI findings are also limited by snapshots of recruitment practices captured through select audio-recorded consultations; as a result, it was not possible to capture what patients had been told before or after the recorded encounter, which, in turn, limited potential to fully understand how the recruitment pathway (and interactions throughout) may have shaped decisions about trial participation. Although resources did not permit this in the NAIROS, case studies of a sample of eligible NAIROS patients' experiences as they move through clinics and interact with different personnel would have provided more in-depth and comprehensive insights into how recruitment plays out in practice. The process evaluation, presented in the next chapter, does, however, provide insight into patients' experiences of the trial, and provided opportunities for triangulation through regular meetings and sharing of emerging findings between the QRI and process evaluation researchers.

Chapter 6 Qualitative process evaluation

Introduction

Surgery and surgical trials are complex interventions, which have multiple components and contextual factors to be taken into consideration.[129] Recent guidance[130] has reinforced the importance of understanding complex interventions as events in systems, recommending attention to context and to understanding how evidence generated might inform decision-making. Qualitative process evaluations can be valuable in this respect, guiding the optimisation of both health interventions and trial processes and supporting implementation.[62,131–133]

Quantitative findings suggest that most patients (56–100%) undergoing septoplasty are satisfied with the outcome.[62,134] However, outcomes of septoplasty on symptoms and quality of life may be more mixed.[43,135] To our knowledge, no studies have investigated qualitatively patient or health professional experiences of delivering and receiving septoplasty.

The aim of the process evaluation was to describe and understand patients' and healthcare professionals' experiences of the NAIROS trial, including the interventions under evaluation, and to identify any factors likely to influence the wider implementation of the trial findings.

Methods

Design

The process evaluation was designed as a qualitative study comprising in-depth interviews with patients and staff (surgeons and research nurses) involved in the NAIROS trial and a thematic analysis informed by normalisation process theory (NPT).[136,137] NPT has been widely applied in understanding the implementation of complex interventions in health care.[137] In the context of the NAIROS, the trial itself (and all associated processes, including those under evaluation) was identified as the complex intervention. NPT incorporates four constructs: coherence (how people make sense of the trial), cognitive participation (whether or not people are willing and able to buy in to implementing the trial), collective action (people's ability to take on the work needed to implement the trial) and reflexive monitoring (people's reflection on the benefits and costs of the trial).[136]

Recruitment and sampling

Participants

At trial recruitment, eligible patients who had agreed or declined to participate in the trial were invited to consent to contact from the qualitative substudy team. Participants were subsequently purposively sampled (site, gender, allocated arm) and approached with further information using their preferred method of contact (telephone, e-mail) and invited to take part in an in-depth telephone interview. A further purposive sample of participants (site, gender, allocated arm, participants discontinuing allocated arm) was recruited to a follow-up interview; this included, but was not limited to, those who had participated in an initial interview. A purposive sample (site, role) of healthcare professionals (surgeons, research nurses) who were involved in the NAIROS trial were also invited to participate in interviews.

The number of interviews conducted was guided by the principles of data saturation,[138] whereby participants were recruited until additional interviews did not seem to generate substantially new information in the context of our developing preliminary analysis. Patients were mainly recruited at two

time points: around the time that they were recruited to the study, and at 6-month follow-up. A small number of additional interviews were conducted at other time points to understand patients' reasons for discontinuing their allocated trial treatment. Patient interviews were conducted between February 2018 and January 2020. NAIROS staff members were interviewed at only one time point: between November 2019 and February 2020 (at the end of trial recruitment).

Data collection

Interview processes

Topic guides were developed based on our own and other existing research (relating to trial recruitment and conduct, and on septoplasty), our theoretical framework (NPT)[136,137] and discussion with the wider NAIROS team. The topic guide was updated during the study on the basis of early interviews and participation in the TMG. All interviews were conducted by an experienced qualitative researcher. Staff interviews were conducted by the researcher who had previously been involved in the QRI. This enabled the selection of participants and the content of interviews to be informed by what was already known about sites. Following an opportunity to ask further questions about participation, verbal consent, using an approved (as part of the REC review) verbal consent checklist, was obtained and recorded at the start of the interview.

Analysis of the interviews

Qualitative data management and analysis

All interviews were audio-recorded, transcribed verbatim and edited to ensure the anonymity of the participants. All transcripts were managed in the qualitative analysis software NVivo (version 12). During data collection, regular meetings were held (between NR and JM/CW) to discuss the preliminary analysis and to make decisions about further data collection.[139] When concerns about specific aspects of trial conduct emerged in the patient interviews, these which were fed back to the wider TMG (via attendance at the monthly TMG meetings or more rapidly by e-mail if necessary) and, when appropriate, to sites. For example, patients in the medical treatment arm highlighted issues with accessing the pharmacy at certain sites, and patients who were planning to travel by airplane raised concerns about the size of the saline solution bottles. In addition to this ad hoc feedback, a presentation on patients' experiences of aspects of trial conduct was given at the investigators meeting in September 2018. This covered examples of positive feedback regarding interactions with NAIROS site staff, examples of patients' preferences being influenced by discussion with NAIROS recruiters, misunderstandings regarding the role of eligibility checks, and positive experiences of both trial interventions. We used thematic analysis with a coding framework to analyse the data.[140,141] The coding framework was developed by two researchers (NR and KL). The framework was developed after reading through several interview transcripts and reviewing previous literature in the topic area of qualitative process evaluations of clinical trials, and with reference to our sensitising theoretical framework, NPT.[136] To refine the coding framework further, two researchers (NR and KL) coded two different interviews independently and discussed their findings. Because most codes were relevant in both patient and staff interviews (e.g. patients described their symptoms of nasal obstruction; staff described how they used these symptoms, together with other factors, when deciding on an appropriate course of treatment), we decided to use the same coding framework for both patient and staff interviews, to facilitate a comprehensive and cohesive analysis.

One researcher (KL) coded all healthcare professionals' and patients' interviews using the same coding framework. Kelly Lloyd and Nikki Rousseau discussed the codes and findings collaboratively, and generated themes through these discussions. After the development of the main themes from the NAIROS interview data, we considered the themes in the context of four core constructs of NPT.[136]

Results

Fourteen staff members (surgeons and research nurses) working on the NAIROS trial were recruited and interviewed across 11 sites. Staff interviews lasted between 24 and 81 minutes. As shown in *Table 21*, 31 patients were recruited. Seven patients were interviewed at two time points, and 23 patients were interviewed at one time point only. One interview was conducted with a patient who declined to participate in the trial. In total, 39 patient interviews were conducted and interviews ranged from 6 to 33 minutes in duration. Sites and participants are labelled (e.g. site 1, surgeon 1) to give an indication of the spread of data; however, to maximise confidentiality, site and participant numbers used in this chapter do not correspond with those used elsewhere in this report.

After analysing both the staff and patient interview data, four main themes were identified: anticipated impacts of the NAIROS trial, making a decision about surgery, experiences of treatment, and reflections on the trial.

TABLE 21 Description of the patients interviewed in the NAIROS (*n* = 31)

Description	*n*
Intervention	
Septoplasty	13
Medical management	16
N/A: dropped out of trial	1
N/A: declined to participate in the trial	1
Gender	
Male	21
Female	10
Ethnicity	
White	28
Asian	1
Other ethnicity	2
Age (years)	
18–30	9
31–40	6
41–50	5
51–60	5
61–70	4
> 70	2
Site number	
1	1
2	10
3	2
5	5
6	2
8	1

continued

TABLE 21 Description of the patients interviewed in the NAIROS (*n* = 31) (*continued*)

Description	*n*
10	3
11	2
12	2
13	2
14	1
Number of interviews	
Recruitment interview only	17
Post-treatment interview only	6
Recruitment and post-treatment interview	7
Declined the trial interview	1

N/A, not applicable.

Note
To preserve participant confidentiality, site numbers in this table do not correspond with site identifiers used elsewhere in this report.

Anticipated impacts of the Nasal AIRway Obstruction Study trial

Views of the NAIROS research question were relevant to both patient and staff motivation to participate in the trial. For staff, this related to how valuable they felt the evidence that a trial would generate might be, whereas patients were more interested in how the NAIROS research question resonated with their own understandings and expectations of the causes of, and treatment for, their nasal obstruction.

A lack of high-quality evidence supporting the use of septoplasty and the uncertainty of its future appeared to motivate some surgeons to take part in the trial:

> *Yes, if we are honest, you know, the evidence base for the septoplasty was almost non-existent … understanding what could benefit them and which patients – having some objective measures to determine suitability was high time.*
>
> *Surgeon 1*

Staff members felt that the research question was appropriate and long overdue in the ENT specialty. They felt it was an important question that needed to be investigated by a robust RCT:

> *In terms of the question it's asking, my feeling was, 'Thank [expletive] somebody is finally doing this properly'. There have been a couple of small studies that have shown some quite interesting results, pointing at patients with post-decongestion unilateral nasal … You know, objective nasal airflow reduction being the patients that benefit. They're small studies, they weren't done in a very rigorous way, so it was hard to be clear that that was a thing that needs to happen.*
>
> *Surgeon 2*

> *I think it's a very good question, and we don't have a formal answer for it without having done a randomised controlled trial. We do an awful lot of operations on the NHS, and that's just from historic, and having the data behind it to say, 'Actually, this is very effective' or, 'This isn't effective' or, 'This treatment is better' is obviously a great way forward. ENT, like a lot of specialties, we're starting to get pressurised by the NHS to justify why we do something, what our action is.*
>
> *Surgeon 3*

There was variation as to whether some investigators felt that the aim of the NAIROS was to provide high-quality evidence for the effectiveness of septoplasty, or whether this was a trial to compare which treatment for nasal obstruction was more effective. One research nurse stated that when they originally took part in the NAIROS they felt that the aim of the trial was to confirm the effectiveness of septoplasty. However, after observing that patients returning for their NAIROS review appointment had positive and negative experiences of both treatment arms, they changed their view and instead saw it as a trial comparing two equal treatments:

> Interviewer: *Did you have any reservations about NAIROS before you started recruiting to it?*
>
> Research nurse 1: *Yes, because with thinking that it was just to confirm what people thought I, kind of, had the reservation thinking that people who were randomised to the medical arm were not getting the optimum treatment.*
>
> Interviewer: *Right. Did that change, then, in terms of …?*
>
> Research nurse 1: *Yes, when people have come back and people have been quite happy with the sprays.*

Several surgeons described wanting the results of the NAIROS to clearly demonstrate which patients are going to benefit from surgery and which will benefit from medical management. In turn, these results could lead to a reduction in the number of unnecessary procedures performed:

> Interviewer: *What would you hope NAIROS to show?*
>
> Surgeon 1: *Show which patients, in these groups, do best for the surgery and which patients, perhaps, can just be managed medically.*
>
> *[W]hat I'm hoping comes out of the trial is probably that septoplasty is useful, but it's useful for certain people and not for everybody, and medical treatment is better for some others.*
>
> *Surgeon 4*

Surgeons also described wanting a more standardised approach to assessing which patients will benefit from septoplasty:

> *If we find that some of the symptoms' scores have a good correlation with people that benefit, or the rhinospirometry measurements and stuff correlate well, then that might be quite a useful way of judging who would be a good candidate for the operation and who might not.*
>
> *Surgeon 4*

However, one surgeon was cautious of the idea of using objective measures for septoplasty referral:

> *I'm not convinced it's [assessment tools] the only thing that you should rely on.*
>
> *Surgeon 5*

The results from the NAIROS trial also had the potential to demonstrate that septoplasty is no more effective than medical management. One surgeon noted that their colleagues were reluctant to be involved in the trial as they felt that the NAIROS trial could threaten the future of septoplasty:

> *I think some people felt threatened by the study because they felt, 'By putting patients in the study, this is all adding to the evidence that's going to take away septoplasty. We're not going to be allowed to do it anymore.'*

> *I was trying to explain to them, 'Well, actually, this is going to produce evidence that might support septoplasty. As far as taking it away, if they're going to take it away, they'll take it away anyway. This is our one opportunity to contribute to potentially preserving the operation, if we can show a benefit.'.*
>
> *Surgeon 6*

Overall, the impacts that surgeons anticipated or desired from the NAIROS trial appeared to influence their motivation to participate.

Patients' motivation to participate in the NAIROS trial was also influenced by their expectations of the impacts of the NAIROS treatment options. Patients' understandings of the cause of their symptoms (e.g. that they had a clear nasal septum deviation associated with a specific injury) and their perceptions of the likelihood of a successful treatment outcome (drawing on prior experience with medical management and on wider experiences of friends and family) affected their views of the NAIROS research question:

> *My first reaction, to be honest, I told her that I would like to have an operation done because, in my personal opinion, if the bone is then tilted towards the side, a medicine cannot cure that.*
>
> *Patient 16*

> *Because I was put in this situation with a traumatic blow to the face, I think, probably, going under the knife was the way to fix it.*
>
> *Patient 18*

> *I was hoping I wouldn't be [randomised to surgery], because a friend of mine, he's just had, basically, the same surgical procedure done, and it's made no difference to him whatsoever.*
>
> *Patient 19*

However, the majority of patients were uncertain as to what the best treatment for their nose symptoms was, and so regarded the NAIROS research question in a positive light:

> *I think people think of an operation as a straightforward thing, but nothing is straightforward, really. It's under a general anaesthetic, it's the dangers that go with it. And with the success rates, as well, they weren't 100% that it would work. So, I thought well, rather than going down the route of the operation, why not try the study, using the spray, and see what sort of success I have from that first. And then, because I had the option to go back for an operation, that was always there in the background, if the steroids failed.*
>
> *Patient 20*

Making a decision about surgery

There was considerable complexity and heterogeneity in terms of both patients' symptoms of nasal obstruction and how clinicians used these symptoms, together with other factors, to make a decision about whether or not to offer surgery.

Staff described a decision-making process that took into account the nature and severity of the symptoms; the length of time these had been experienced; the nature of symptom onset (whether or not it was associated with a particular injury or other event); whether or not symptoms varied seasonally; and the structure of the nose, including the degree of deviation and where the deviation occurred.

Patients presented with a range of different symptoms in clinic, including nasal blockage, trouble sleeping, snoring and frequent nosebleeds (*Table 22*). Several patients could recall an injury that had damaged or broken their nose, whereas others did not remember such an incident.

TABLE 22 Patients' descriptions of their symptoms that led to them being referred to the ENT clinic

Patients' symptoms	Example from patient
Feelings of nasal blockage	*My right nostril is pretty much useless, it's blocked 99% of the time* *Patient 1*
Difficulties sleeping	*More recently, it had got to the stage where it was causing me a lot of difficulty at night sleeping* *Patient 2*
Snoring	*I started snoring and I'd never snored in my life, and obviously it's waking me up in the middle of the night, you know?* *Patient 3*
Dry mouth	*And my nose would just shut down, and I'd end up breathing through my mouth, and wake up in the middle of the night with a mouth that's like sandpaper* *Patient 2*
Frequent nosebleeds	*I had frequent nosebleeds throughout the day; I could just randomly have one without any trauma to the nose* *Patient 4*
Recurrent sinus infections and migraines	*I was constantly getting sinus infections. I was very prone to sinus infections. I used to get a lot of headaches* *Patient 5*
Olfactory dysfunction	*It is not that good because I can't really smell food. The past year I haven't been able to smell food properly* *Patient 6*
Difficulties exercising	*When I go running, or if I do exercise, then it's slightly harder than what I remember* *Patient 7*

Staff members also reported a complex pattern and history of symptoms presented by patients in clinic:

> *I suppose there are the people that are not quite congenital, but something has happened very early in life and they have grown up with it to some extent. Quite often they don't complain that much, because they have never known anything different. Sometimes it's because they have developed a bit of an allergy or something, and maybe the septum is not the whole story.*
>
> *Then I suppose quite a few of them are traumatic, and that can be people who play rugby or football or things like that, or the younger core who go out on a Friday night and have a fight. There are a few of them around.*
>
> *Then you probably move on to older people, who I think have probably always had a bit of a septal deviation, but the cartilages have been quite firm. Then they get to 50, 60 or a bit more and everything starts to droop a little bit, and then they have a problem.*
>
> *Surgeon 4*

The heterogeneity across patients seen in clinic and the lack of standardised measurement tools for assessing patients' septa and symptoms has led to a subjective approach among clinicians with regard to septoplasty referrals:

> *We don't really have a good way of objectively assessing the degree of deviation of the septum. So it did come down to, pre-NAIROS, essentially just looking in the nose and seeing how twisted it was and it is a challenge there because nobody has a completely straight septum and some patients will have a septum that's twisted into the opposite nostril rather than the affected nostril. So the decision to operate was not really based on just the degree of deflection of the septum, it was the additional symptoms as well that the patient's complaining of.*
>
> *Surgeon 7*

> *Examining the nose, I will be looking to see if they actually do have a septal deviation and if, in my mind, I think it's significant enough to cause the degree of symptoms that they have. If they have such a mild deviation and such a significant degree of symptoms, I wouldn't necessarily correlate the two. I'd be very wary about offering them surgery because their expectations are that all those symptoms that they're complaining of will improve, whereas I find that they don't tend to. Structurally, it has to be significant enough for me to think, 'I can make a difference'.*
>
> *Surgeon 6*

Clinicians also displayed subjective decision-making in relation to managing patients' symptoms. Most surgeons reported that they often recommended medical management to patients before offering them surgery. Surgeons whose current practice more closely followed the protocol of the NAIROS may have also been more inclined to take part in the trial:

> *Personally, I don't think it's changed what I do. I've always maintained giving them proper medical treatment first. That's, I think, partly why I was quite happy to buy into the study, because it followed my normal practice more or less.*
>
> *Surgeon 6*

However, some clinicians stated that, in routine care, they would often refer patients straight for surgery if their septum was perceived to be highly deviated, or if they had a particular incidence of a traumatic injury:

> Interviewer: *And in terms of the reasons why you would put people straight through to surgery?*
>
> Surgeon 8: *Well might be the GP letter, it might be the patient's history, you know, 'I could breathe alright up my nose, then I fell on it' ... so that chronological context would be helpful. And just the severity of some people have a very twisted septum that you can see they've got a vertical fracture line that's effectively presenting– the bottom end of the septum is a door across one nostril so those ones you'd be more inclined just to go for surgery.*

In the trial, surgeons who felt that particular patients were more in need of having surgery straight away, rather than potentially being prescribed medical management, may not have recruited these patients to the NAIROS trial for this reason. Therefore, the trial population may not have included patients with the most severely deviated septa:

> *I'm aware that some colleagues have not necessarily recruited the most, well when I say– anecdotally, I'm aware that some colleagues have not necessarily recruited the most severe nasal septal deflections to the study. So I think we may not necessarily be looking at the entire population of deviated nasal septums.*
>
> *Surgeon 7*

Generally, despite the high heterogeneity in staff criteria for referring patients for septoplasty, surgeons felt that the eligibility criteria in the NAIROS protocol was appropriate for the trial:

> Interviewer: *[A]nd you are happy with the patients who were supposed to be put into NAIROS, the eligibility criteria?*
>
> Surgeon 4: *Yes. There was nobody we recruited that I wasn't happy to operate on. I think that's the main thing.*

There was also variation in other aspects of ENT routine practice, including whether or not clinicians used any outcome measures (e.g. SNOT-22, NOSE), and whether or not they followed up with patients after their operation outside the trial setting:

> *In general we wouldn't have employed any objective testing, I wouldn't have done any patient-reported outcome measures, I would have just proceeded with the operation.*

Experiences of treatment for nasal obstruction

This theme relates to the experiences of delivering (staff) and receiving (patients) treatment for nasal obstruction.

Performing septoplasty: variation in surgical practice

Surgeons reported that septoplasty was an operation that they had learned to perform independently relatively early in their surgical ENT career. Septoplasty was described as a commonly occurring operation in ENT practice, but one that could be difficult to accomplish well:

> *It's one of those operations which people would say is an intermediate-skilled operation, but actually to do it well is pretty skilful.*
>
> *Surgeon 7*

> *I suspect a lot of people will imagine a septoplasty is a simple procedure, and it's one of the first operations ENT surgeons learn to do by themselves. It's actually quite a potentially complicated operation to get perfectly right, just because there are lots of different areas that may need addressing.*
>
> *Surgeon 3*

Variation in practice was not only limited to the criteria for septoplasty referrals. There was also variation in how surgeons carried out septoplasty, with one surgeon describing that their surgical technique changed as they gained more experience carrying out the operation:

> *Anatomical knowledge of knowing where the airflow manoeuvre is the narrowest. The subtleties, as you gain more experience, you realise it's not just the septum which causes problems with nasal airflow, there is also the soft tissue and the cartilages in particular, the lateral cartilages which can also have an effect, and it's identifying those and addressing those subtleties which give a better outcome for the patients.*
>
> *Surgeon 3*

Another key point of variation among surgical practice was the surgeon's threshold for offering turbinate reduction alongside septoplasty:

> *So for me I think I have a relatively low threshold for offering turbinate reduction at the time of septal surgery. Patients are clearly having a general anaesthetic anyway to correct the septum, reducing the bulk of the turbinate in my opinion is going to lead an improvement in the – an additional improvement in the airway, and therefore I would have generally offered it if a turbinate was large.*
>
> *Surgeon 7*

The large variation in surgeons' practice of septoplasty and turbinate reduction led to the NAIROS protocol being designed to be more flexible in regard to surgeons' practice. This flexibility in the protocol regarding surgical procedure was welcomed by surgeons who took part in the trial:

> *Turbinate reduction was optional, so it was nice to have the ability to do that.*
>
> *Surgeon 1*

> *The only one thing I had to do differently, which I was compelled to do because of study design, was … There were some patients who did have, either, allergic rhinitis or intrinsic rhinitis. Their lining, their turbinates were very congested. I would ordinarily have reduced both turbinates, on each side. The study restricted me to only doing the one. So there was a little bit of restriction to my normal practice in that. As far as surgical technique, and what I did, I didn't do anything different and I didn't feel curtailed.*
>
> *Surgeon 6*

Patients' experiences of treatment

Patients who were randomised to medical management had differing opinions on their experiences of this treatment arm; some patients reported side effects from the sprays whereas others did not. Several people in the medical management arm mentioned nosebleeds. This is consistent with the data on AEs (see *Appendix 1*, *Table 67*), which show more nosebleeds reported in the medical management arm. One participant reported that they had been advised that their nosebleeds may have been associated with the mode of administration (inserting the spray bottle too deeply), and other people highlighted that using the spray was difficult when there was an obstruction:

> Interviewer: *How did you find the nasal sprays?*
>
> Patient 8, medication: *To be honest, it didn't do good for me at all … No, it sort of gave me two nosebleeds. I've never experienced nosebleeds before, so I didn't get on well with them at all.*
>
> *Obviously, when you're trying to put a nasal spray up a nose that doesn't allow anything to go up it, it's difficult. But I persevered.*
>
> *Patient 15, medication*
>
> *I was fine with them. At first a bit weird, you know these sprays that went down the back of your throat, you feel them going down your nose and then down the back of your throat, you have to put your nose up in the air, but you feel it. I got used to it, and when you're used to it, it's normal.*
>
> *Patient 3, medication*

Medical treatment could be a burden to patients (albeit a usually minor one). In addition to potential discomfort and difficulties with application, several patients reported that remembering to take the medicine was burdensome, although many had established a routine to help them remember, for example placing the bottle next to their toothpaste. During the first 6 months of the NAIROS trial, medical treatment was free for patients, but this would not be the case after this period, and this was mentioned as being something that would be unwelcome over the longer term. A few people reported minor issues with obtaining their supply of NAIROS medicines; although, in routine care, patients would not need to attend hospital pharmacy, long-term use of medications would imply a periodic need to obtain new supplies. This again represents a small additional burden (particularly given that the NAIROS population was generally younger, of working age and might not otherwise be frequent users of health care):

> *[W]hen you're there and they show you this stuff. It's like, 'Right. It's that up your nose', for however long. I could do without that, basically.*
>
> *Patient 16*
>
> *I mean, there was no cost out … no cost towards it, so that's even better. You don't want to pay for the medicine all the time.*
>
> *Patient 3*

We also explored the experiences of patients randomised to septoplasty. Typically, patients who received the operation described the experience as neutral or positive:

> *Yes, surgery was fine, all well-handled, everything was explained to me again, and I have no adverse comment whatsoever, everything went well.*
>
> *Patient 8, septoplasty*

However, several patients experienced notable painful side effects following the operation:

> *After the surgery it was painful. I also got sent home without any nasal wash or anything, which Dr [name], when I went for my follow-up, he said I should have had that when I left the hospital.*
>
> *Patient 9, septoplasty*

> *Well, I was in a lot of pain. Pretty much every day was just constant dripping from my nose afterwards. Then I think it was exactly a week later I ended up having to go into A&E because I woke up in, basically, a pool of blood.*
>
> *Patient 10, septoplasty*

Several patients stated that they would have liked further information on recovery and aftercare following surgery. Patients described feeling uninformed on these key aspects of their treatment and would have benefitted from knowing what they could or could not do during recovery (e.g. blow their nose):

> *To be honest with you, I got no information at all after the operation. I was told to do the nasal washouts and that was pretty much it, but I got no other information. When I rang the hospital about it, all I got was, 'Well, yes, it's just a water solution that you're supposed to be using'. That was it. I don't know. Even painkillers and stuff like that, obviously I had nothing, so it was just paracetamols and stuff in the house. To me, I feel it would have been better if I was given something a bit stronger initially.*
>
> *Patient 10, septoplasty*

> Interviewer: *Would you have liked information about anything else?*
>
> Patient 5, septoplasty: *I think the follow-up more than anything. I was a bit curious, I've had to do a bit research myself obviously now I'm on the, on the healing side. It's like, 'Well, when can I blow my nose? How can I manage this? When can I start sinus flushing and stuff?'. Because it's really, really blocked. So more on the aftercare would have been a bit better.*

The interviews with patients also explored whether or not they felt that their allocated treatment was successful in reducing their symptoms. We found that patients in both arms described differing levels of success with their treatment allocation. Experiences of the medical treatment arm varied. Some people felt that there were no beneficial effects and/or that any marginal benefits were outweighed by the disadvantages of use (associated pain and/or nosebleeds); these patients typically rapidly discontinued use and sought surgical intervention:

> *It wasn't long into it, I think. I'd been on it for 3 weeks or something and I decided to contact them .... They asked me if I'd want to carry on for a little bit longer with the nasal spray, so I tried for another week, but it was just too sore. I messaged them saying that I'd like to be reassessed for the surgical path .... I didn't really see any changes at all, not for the better and not for the worse either. It was just painful taking the nasal spray.*
>
> *Patient 1*

Other patients felt that the spray did offer benefits, albeit small and/or short-lived. Some people reported that the beneficial effects typically lasted a few hours after application, suggesting that the benefits were more linked to the flushing effect of the saline spray, rather than an anti-inflammatory effect of the steroid. However, even these benefits might be worth having; for example, they enabled one person to obtain adequate sleep when this had not been possible prior to treatment:

> *[I]f I put that saline water up and put the steroid spray in, it gives me relief a little bit. For a couple of hours, it's very good ... After that, it goes.*
>
> *Patient 16, medication*

> *With the medication I'm taking now, it will give me temporary, 2 or 3 hours, relief and that's it. Especially the medication I'm going through now, it's helping me to have a good night's sleep, which I was not having for a very long time.*
>
> *Patient 11, medication*

Other people obtained more substantial benefit from the spray. One person reported significant improvement and was informed at their clinical review that their enlarged turbinate had shrunk as a result of treatment, providing a clear mechanism to explain the improvement experienced:

> Interviewer: *How has your breathing been since you started on the sprays?*
>
> Patient 11, medication: *Actually, I was waiting for this question to come up. Much better, but I still get a little bit of congestion.*
>
> *I didn't really have any side effects; it really helped me. I didn't have any symptoms of hay fever throughout the summer at all, which was great. When I went to see the consultant at the end, she said that, I think it was turbinate up my nose or something had been quite swollen, but I think the steroids had shrunk them a bit. So it seemed to really have cleared up my airways.*
>
> *Patient 21, medication*

Septoplasty also had varying levels of success. However, those who found the operation effective typically experienced quite high levels of success, with patients feeling that they had experienced a massive reduction in their symptoms following the operation:

> *So, you know, ultimately, having the septoplasty, although it was uncomfortable and not particularly pleasant, it has been great. I can now breathe.*
>
> *Patient 12, septoplasty*
>
> *I'm still having trouble sleeping, but … I don't think it's down to my nose. In fact my breathing is a lot better now.*
>
> *Patient 13, septoplasty*

However, some patients who underwent surgery felt that the operation resulted in little to no change in their symptoms:

> *Well, the operation itself was fine, yes, but unfortunately it hasn't worked.*
>
> *Patient 10, septoplasty*
>
> *The surgery itself was fine. The results I'm not particularly happy about because I'm feeling no change at all in the way I'm breathing.*
>
> *Patient 1, medication (requested septoplasty)*

Reflections on the trial

Overall, the trial recruited the target number of participants. A number of potential facilitators of the NAIROS trial that contributed to its successful recruitment were identified by participants (*Table 23*). Challenges in relation to the set-up and running of the trial are presented in *Table 24*. Participants also identified a number of ways in which they had reflected on or made changes in practice as a result of their participation in the NAIROS.

TABLE 23 Suggested facilitators of the NAIROS that helped the trial recruit to target, and examples from participants

NAIROS facilitators	Example from participant
Research nurses	*So, the biggest key to success which I'm going to take away is the research nurse is absolutely essential. I naively thought I might be able to struggle through that one, and I would never have coped* *Surgeon 3*
Surgery offered after 6 months	*I think it was very important, because I was willing to give the nasal sprays a go again, but I also knew within a year of it, I would get the surgery to definitely fix it anyway* *Patient 14, septoplasty*
Team effort	*We've worked really well as a team. We are a small team, and we kind of all know what everybody is doing, so we just kind of get on with it and it works. Yes, we've worked really well together* *Research nurse 2*
Established medication	*The only concern I had was, was this a trial of the medication or was this a process trial? I wasn't happy with putting medical stuff in that hadn't been tested* *Patient 15, medication*
QRI	*I think the QRI involvement has been key actually to getting us to where we are with our recruitment numbers* *What's been more important in that is the involvement, the ideas, the focus on recruitment that QRI have brought* *Surgeon 7*
Information resources	*I think it was really good, because it was the right amount. I think any more, then people would probably not want to read it to the same extent. Any less, you couldn't really have any less because it contained all the right information* *Patient 7, medication*
Effective communication of clinical equipoise	*I totally took my decision on the basis of what [consultant] said to me, 50% to 70% chance of getting the normal breathing back through the operation, which can be cured, almost the same ratio, with the medicine. I thought, 'Fine, I'll try the medicine first'* *Patient 16, medication*

TABLE 24 Challenges when implementing the NAIROS, and examples from participants

NAIROS – barriers	Example from participant
Patients' comprehension of randomisation	*I assume that, depending how many points I totalled up, determined whether I would need the spray or the surgery* *Patient 17, septoplasty*
Complicated consent process	*The consent process was, perhaps, a little bit cumbersome with the three separate consent points. I know, this end, that we got into a, sort of, routine for that, but I think that could be streamlined into just one single consent* *Research nurse 1*
NAIROS database	*It's not very user friendly, I would say, and there are quite a few glitches in the database* *Research nurse 2*
Challenges with surgery offered later	*Then he really, really wasn't happy about that at all, because our waiting list at the moment is about 70 weeks' for septoplasty. It has gone up massively* *Research nurse 3*
Issues with follow-up	*A couple of days before the date I'll be like contacting them, 'Please make sure you fill in the questionnaires and send them back by this date.' kind of thing. That's been quite hard to encourage the patients basically, especially the surgical ones* *Research nurse 3*
Colleagues not proactive with recruiting	*Well I expected a bit more buy-in because I did get a lot more verbal support from my colleagues initially* *Surgeon 4* *I did expect my colleagues to refer more patients to me, but it didn't turn out as I hoped* *Surgeon 6*
Logistical problems with NAIROS recruitment clinics	*More of an issue was that there weren't enough clinics, there were too many people who could be … too many potentials to fit in to the clinics* *Research nurse 1*
The NAIROS as a CTIMP	*This being a CTIMP type of study, you can't just hold the clinics anywhere you like, you have to have access to pharmacy* *Surgeon 8*

What worked well in the Nasal AIRway Obstruction Study

Several consultants mentioned the key role of the research nurse in delivering the trial and facilitating recruitment of patients (see *Table 23*). Staff members also highlighted the importance of having a research team at site that worked well together, as this benefited site set-up, the running of the trial and recruitment. Staff also cited the involvement of the QRI team as an important contributor to the successful recruitment to the NAIROS trial. Patients praised the information resources for the trial, which they felt described the trial clearly.

The treatment options provided appeared to be a contributing factor to the trial recruiting well. For example, several patients reported that they would have been reluctant to take part if the trial was testing new medication. In addition, there were benefits to the medical management arm explicitly including the possibility of deferred surgery. Patients felt that they had nothing to lose by taking part in the trial because, at some point, either within 8 weeks or after 6 months, they could still undergo septoplasty.

Challenges with the Nasal AIRway Obstruction Study

Participants noted several challenges when implementing the NAIROS, and identified aspects of the NAIROS that they would have changed on reflection. Challenges for sites included issues with using the NAIROS database, the consent forms being overly complicated, problems with collecting patients' follow-up data, logistical issues in organising recruitment at clinics and lack of team effort from some surgeons' colleagues at site. There were also issues in practice relating to when patients could receive septoplasty once they had completed 6 months of medical management. One staff member described how the site's waiting list for septoplasty had increased from approximately 4 months at the beginning of trial to > 16 months at its end point, leading to frustration when one patient was not able to have surgery after the medical management arm as quickly as they had anticipated.

Across a small proportion of patient interviews, we also noted issues with patients' comprehension of the trial randomisation process. Two patients suggested that the reason they were allocated to their treatment arm was because of the scores they obtained on eligibility or baseline assessment tools. In addition, one patient thought the trial was offering only medication as the initial means of treatment, and was unaware that they could have been randomised to the surgical arm.

Overall though, most staff members and patients were pleased with how the trial was designed, and many felt that they had little to no feedback to provide on the trial:

> *I don't think anything else could've been done differently. I think it was well supported and I think it was designed as well as it could be for a difficult question, for something that's a well-established operation.*
>
> *Surgeon 6*

Furthermore, the majority of patients demonstrated a good level of understanding of the randomisation process, and of the trial itself.

Changes in practice during and after the Nasal AIRway Obstruction Study

One surgeon noted that, during recruitment, they noticed issues with several patients' comprehension of random allocation. In response to this, the surgeon changed their practice to check if the patient would be comfortable with both treatment options:

> *One of the things I did learn was the difference between saying to someone, 'Are you happy to be randomised?' and saying to them, 'If you get randomised to X, are you happy to stay with X?' They're the same thing on a logical basis, but in reality they're slightly different questions for patients. I think asking that question ... Certainly, if I'm recruiting to something like this, I will definitely be doing that in the future because I think you got some surprising answers from that sometimes.*
>
> *Surgeon 2*

Following the NAIROS, several surgeons noted that there were aspects of the trial that they were considering implementing into their routine practice, such as particular outcome measures (e.g. NOSE). However, they were waiting for the trial results first before they changed their current practice:

> *The NOSE score is useful. Whether I would change to that, or stick to the SNOT, I don't know. I think I'd be more keen to see how useful it is when we actually look at our post-NAIROS data to actually see, 'How valid is it? How useful is it with these sorts of patients?' before I definitely change practice.*
>
> *Surgeon 6*

Other aspects of the NAIROS trial that surgeons were planning to incorporate into their routine care included the recommendation to patients of frequent saline douching:

> *I didn't tend to use the saline douching as much as the protocol did, I must admit. I tend to now, because I sort of got used to the study protocol and I think, 'Yes, that makes some sense'. Beforehand, I tended not to give the saline douching as much unless they were complaining of a lot of post-nasal drip.*
>
> *Surgeon 2*

Discussion

This qualitative process evaluation of the NAIROS trial identified considerable variation and complexity in routine clinical decision-making about septoplasty, in terms of which patients should be offered surgery in the place of medical management for nasal obstruction, and in how surgery was conducted. Surgeons recognised this diversity; they hoped that the NAIROS findings would help to guide future decision-making, and they valued the flexibility that the NAIROS protocol offered regarding surgical approach to septoplasty (e.g. regarding turbinate reduction). Among patients, there was a diversity of presenting symptoms and experiences both prior to and following receipt of their allocated treatment. Trials comparing very different interventions can be challenging to recruit to,[142] with 1 in 5 surgical RCTs discontinued early and 1 in 3 completed trials remaining unpublished.[143] The NAIROS trial (comparing medical with surgical management) recruited its target number of participants. Possible reasons for the success of recruitment in the NAIROS trial include the following: surgeons felt that there was value in addressing the NAIROS research questions; the type of treatments the trial was comparing, as these involved established rather than novel therapies, and a clear route to surgical treatment was communicated in the event that those randomised to medical management did not obtain symptom relief; the effective communication of clinical equipoise in the trial; and the teamwork of the site staff. Challenges to implementing the trial were also identified, including continuing confusion among some patients regarding aspects of randomisation (e.g. the role of the eligibility criteria). To understand further the key barriers to and facilitators of trial implementation, we have considered the results of the NAIROS qualitative evaluation in relation to the core constructs of NPT (coherence, cognitive participation, collective action and reflexive monitoring).[136]

Coherence: how people make sense of the Nasal AIRway Obstruction Study trial

Healthcare professionals considered the research question of the NAIROS to be of great importance to the field of septoplasty, which had previously suffered from a lack of high-quality evidence. In usual practice there were variations in decision-making for septoplasty, including how septum deviation was assessed and which patient symptoms were considered important. This variation in current practice appears to be due to the range of symptoms patients present with in clinic, and the lack of valid and standardised methods for septoplasty referral. However, most surgeons felt that medical management could be a valid alternative to septoplasty for at least some patients. Overall, clinicians described the NAIROS protocol positively, owing to its consistency with current practice, its suggested criteria for assessing eligibility of patients and the flexibility with regard to the surgical technique it allowed them to employ (e.g. optional turbinate reduction).

Health professionals had subtle but important differences in terms of what they understood the aim of the NAIROS to be. Some surgeons believed that the aim of the trial was to provide high-quality evidence for the effectiveness of septoplasty to ensure its future funding. In contrast, several surgeons believed more strongly in the clinical equipoise of the trial; these surgeons hoped that the findings of the NAIROS could help to identify which patients benefit from septoplasty and which benefit from medical management. Generally, patients demonstrated a good level of understanding of the trial, and used the NAIROS information resources (e.g. leaflet, website, digital versatile disc) well to understand and make sense of the trial. However, there were instances when patients' sense-making of the trial did not align with the trial itself. For example, as in previous studies, a small number of patients demonstrated a lack of understanding of the computer randomisation process.[144]

Cognitive participation: whether or not people were willing and able to buy in to implementing the trial

Many surgeons were motivated to take part in the NAIROS because they felt that the results could provide the high-quality evidence needed to ensure the future of septoplasty, whereas other surgeons felt that the results could reduce the number of unnecessary septoplasties conducted. However, there were also difficulties with healthcare professionals buying in to the trial, with some surgeons struggling to convince their colleagues of the value of the NAIROS.

In addition, there were instances of healthcare professionals not adhering to the trial inclusion and exclusion criteria, which may have led to patients with a highly deviated septum not being approached to take part in the NAIROS.

Patients were positive about the fact that the trial was testing established medication and surgery, rather than new and experimental treatments. Previous studies have identified patients' preference for a particular treatment arm as a barrier to trial recruitment.[131,145,146] By offering patients enrolled in the medical management arm the option of being put on the septoplasty waiting list after 6 months, this may have minimised the effect of patients' preference on recruitment rates.

Collective action: people's ability to take on the work needed to implement the Nasal AIRway Obstruction Study trial

Most staff members were positive about trial implementation and felt that the research team collaborated effectively together to execute the trial at site. The involvement of the QRI in the NAIROS was also cited by staff as having a positive influence on recruitment rates. As in previous studies,[148,149] research nurses in particular were highlighted by surgeons as being essential to the implementation of the trial at their sites. However, participants also described several challenges in relation to implementation. For example, there were issues with retention of patients at follow-up and logistical difficulties organising NAIROS recruitment. Furthermore, colleagues' initial enthusiasm about the NAIROS trial did not always translate into action during the trial, such as aiding with screening and recruitment of patients.

Reflexive monitoring: people's reflection on the benefits and costs of the trial

One staff participant described how their views of the treatments changed during the trial. Originally, they believed that surgery was much more effective than medical management; however, after witnessing a number of patients experience symptom relief from the steroid sprays, they came to view the trial as comparing two more equal treatments. Although the NAIROS quantitative data show that, as a group, those randomised to septoplasty experience more improvement than those randomised to medical management, the qualitative data demonstrate nuance and variation at the level of individuals, with some participants not observing any improvement following septoplasty and others experiencing benefit with medical management. For one patient, visible changes in turbinate size were felt to be attributable to steroid use and to account for improved nasal air flow. Steroid treatment is an established treatment for enlarged turbinates,[150] but further research is needed to clarify the role

of medical management in the presence of a deviated septum. Patients with septal deviation could clearly understand how straightening the deviation might improve airflow, but sometimes struggled to understand a comparable mechanism for medical management. Providing a mechanism that includes observable changes in nasal structures ('shrink') may be more consistent with patients' understandings of nasal obstruction in the presence of septal deviation than broader terms like 'decongestant'.

Previous quantitative research has shown mixed findings in regard to patients' rates of satisfaction and quality of life following septoplasty.[43,62,134,135] In the NAIROS interviews, many patients suggested that information on recovery post septoplasty was lacking, which led to them feeling unsupported following surgery. Inadequate information on aspects such as recovery has been linked to dissatisfaction with surgery and increased anxiety levels among those undergoing day surgery.[151] More comprehensive information on recovery post septoplasty might increase patients' feelings of support and satisfaction with surgery. Medical management was generally well tolerated in the trial; however, a number of patients did experience nosebleeds and/or discomfort when using the spray. Patients incorporated the sprays into their daily routines to help them remember to use them, but some expressed concerns about the potential cost and burden of long-term medication use. In interviews no-one mentioned potential side effects of steroids, or specific concerns about the use of steroid medications long-term, but these have been a concern in other populations[152] and might emerge as a greater concern in the medium to long term.

Overall, many healthcare professionals did not plan to change their current practice until the results of the NAIROS were released. Even then, many felt that the NAIROS matched their current practice quite closely and were considering implementing only a small number of changes, such as the use of particular outcome measures. One surgeon also described how taking part in the NAIROS had altered their recruitment technique for future trials.

Summary of findings and implications

- Pre the NAIROS, clinician decision-making for septoplasty was heterogenous, with a mixture of standardised measures (e.g. NOSE, SNOT-22), history, symptoms, prior trial of medical management and anatomy being variously employed by surgeons in different centres.
- Surgeons would value guidance to help them identify patients who might benefit from septoplasty and those who might benefit from medical management.
- The decision by the trial team to incorporate the option for deferred surgery in the medical management arm appears to have been a key factor in the successful recruitment to the NAIROS trial.
- Many patients were willing to try medical management once it was explained that surgery was not guaranteed to provide symptom relief, and valued the opportunity to see whether or not surgery could be avoided.
- For some people, medical management did deliver an improvement in symptoms, with a reduction in turbinate size being provided as one possible mechanism of action.
- Some people found the sprays difficult to use; one person was advised that their nosebleeds were associated with using their spray incorrectly. Personalised guidance on spray use, taking account of any abnormal nasal anatomy, might enable optimal use of this intervention in this patient group.
- Long-term use of steroid sprays would be associated with an element of treatment burden, with patients mentioning cost, the need to remember to use the spray and minor inconvenience of obtaining supplies as specific burdens.
- In spite of the strong overall effect in the NAIROS, some individuals did not experience noticeable benefit from surgery. There is a continued need to understand the varying subgroups experiencing nasal obstruction so that patients do not undergo surgery unnecessarily and obtain treatment that does improve their symptoms.

Strengths and limitations of the qualitative study

A strength of the qualitative study is that we recruited patients from multiple trial sites, from different age groups and at different time points in the trial pathway. However, the sample was less diverse in terms of ethnicity. In addition, we recruited and interviewed multiple surgeons and research nurses from a range of trial sites. An important limitation of the study is that we recruited only one patient who declined the trial. Therefore, we were unable to explore the factors that influenced patients' decision not to participate in the NAIROS.

Conclusion

Prior to the NAIROS, decisions regarding the appropriateness of surgery for individual patients were made on the basis of a complex and largely subjective combination of symptoms, history and patient anatomy. Surgeons indicated that they would welcome clearer criteria to guide decision-making.

Although trial findings show that, as a group, participants in the surgical arm experience more improvement than those in the medical management arm, the qualitative study demonstrated that individual experiences varied. Some participants did not observe any improvement following septoplasty and others experienced benefit with medical management. Research should continue to explore and understand this variation. Patients undergoing medical management might benefit from individual advice regarding application of the sprays, taking into account distorted anatomy, to maximise effectiveness and reduce side effects. Although most patients were able to incorporate spray use into their daily routines, long-term spray use was perceived by some to be burdensome. Some participants undergoing septoplasty reported being underprepared for the immediate post-surgery period; better information and support could improve their experience.

Chapter 7 Discussion

Septoplasty is an operation carried out to correct a deviated nasal septum predominantly for functional purposes. It is used in the treatment of conditions, such as a blocked nose, snoring and sleep disruption, that fail to respond to conservative management. There is an absence of nationally or internationally accepted guidelines to inform clinicians and commissioners about this procedure, whose indications are practice based rather than evidence based. Van Egmond *et al.*[58] published the only prior RCT of this surgical procedure in 2019. The outputs of the NAIROS make a substantial contribution to the evidence base of the clinical effectiveness and cost-effectiveness of septoplasty among adults with a deviated nasal septum and associated nasal obstruction. The NAIROS demonstrates that septoplasty, with or without turbinate reduction, results in a significantly greater improvement in patient-reported outcomes at 6 months than a defined medical regimen of nasal steroid and saline sprays, and this improvement is sustained to 12 months.

The NAIROS RCT was a pragmatic trial reflecting current NHS pathways for patients with nasal obstruction, nasal blockage or nocturnal nasal symptoms deemed likely to be the result of a deviated nasal septum by the investigating clinician.

Concerns regarding surgical efficacy and cost-effectiveness mean that access to septoplasty surgery is subject to geographic variation across Clinical Commissioning Groups in England and Wales in particular.[153,154] The NAIROS RCT was a superiority trial designed to meet the commissioning brief set out by the NIHR Health Technology Assessment (HTA) programme (14/226). This mandated a RCT with a non-surgical arm whose outputs should include measures of nasal function, resolution of symptoms, disease-specific quality-of-life measures, AEs and cost-effectiveness over a minimum 12-month follow-up period.

The primary goals were to assess the magnitude of septoplasty risks and benefits and to stratify for baseline severity and gender, as female gender might predict worse outcome.[155] Inferior turbinate surgery is frequently performed alongside septoplasty, but, in the absence of high-quality evidence for the additional benefit of this surgery, clinicians' turbinate practices vary. The NAIROS trial investigators reached a consensus that turbinate surgery should be performed according to the clinical judgement of individual patient requirements. We predefined the 9-point difference in overall SNOT-22 scores at 6 months to represent the MCID. Recruitment to surgical trials can be challenging; our team applied prior knowledge of running RCTs to the NAIROS.[100,156] The QRI team at the University of Bristol [URL: www.bristol.ac.uk/population-health-sciences/research/groups/social-sciences-health/quintet/ (accessed 16 February 2022)] was commissioned to understand the NAIROS recruitment processes and barriers to and facilitators of recruitment, to suggest improvements and to work with the TMG and site investigators on the implementation of those improvements. The trial aimed to complete recruitment by 31 May 2019, but delays in set-up resulted in the trial achieving full recruitment on 5 December 2019.

The onset of the COVID-19 pandemic resulted in the suspension of all face-to-face clinics from 30 March 2020; therefore, remaining trial participants were invited to complete primary and secondary outcome measures remotely. By then recruitment had been achieved and all trial interventions had been completed. Details of AEs were collected remotely by telephone at the 6- and 12-month follow-ups.

Statement and interpretation of results

Clinical effectiveness

The NAIROS demonstrates that septoplasty, with or without turbinate reduction, is a highly effective procedure with evidence that it may be considered cost-effective at 24 months.

The primary analysis was ITT based on a sample of 378 participants, comparing SNOT-22 over 6 months from randomisation to initial follow-up, adjusting for baseline severity (NOSE score), baseline SNOT-22 score and gender. A 6-month interval was chosen as a suitable compromise, allowing sufficient time for surgery to be performed and wound-healing to take place, yet ensuring a timely primary outcome assessment to minimise default from follow-up. As stipulated in the commissioning brief, clinical effectiveness and cost-effectiveness were also assessed at 12 months.

The baseline characteristics of the NAIROS recruits were balanced between the treatment arms (see *Table 3*). Males comprised 67%: septoplasty is known to be more commonly undertaken among males of middle age as a result of septal deviation caused by assault to the face and sporting injuries.[17] A peak age in mid-adulthood among participants is to be expected for similar reasons. There was a significant preponderance of the white ethnic group (88%), as expected from existing UK census data.[157]

Overall, the improvement in SNOT-22 score in the septoplasty arm occurred notably earlier and was greater than expected; this was sustained over the trial period. A more modest improvement from 6 to 12 months was noted in the medical management arm, even after removing those participants who withdrew and had non-trial septoplasty. Those who withdrew and who underwent non-trial septoplasty had an appreciably greater reduction in SNOT-22 score at 12 months.

The primary analysis indicated a greater reduction of an average of 20 points ($p < 0.0001$) in SNOT-22 symptom severity score in the septoplasty arm than in the medical management arm at 6 months (see *Table 6*). In addition, the lower limit of the 95% CI was −16.4 points, substantially in excess of our a priori MCID of a 9-point reduction in SNOT-22 scores post treatment. Additional treatment efficacy analyses adjusted for covariates all showed similarly positive impacts of surgery over medical management (see *Figure 8*).

The impact of baseline severity as measured by the NOSE score was evident, demonstrating greater SNOT-22 scores at the primary outcome point with increasing baseline severity. This was accounted for by the inclusion of the baseline SNOT-22 scores as a covariate. The coefficient for this variable was highly significant and close to 0.5, meaning that, at 6 months, SNOT-22 scores were approximately half what they were at baseline (holding all other factors constant). The effect was mirrored in both genders by the subgroup analysis of paired primary outcome data to assess individual changes in SNOT-22 scores by a STEPP analysis (see *Figure 16*). Several retrospective studies[158,159] have noted a similar impact of baseline severity on post-operative subjective nasal obstruction, but without robust quantification. This novel and important NAIROS analysis enables clinicians to quantify expected outcome improvements of patients contemplating septoplasty, with or without turbinate reduction, predicated on the baseline NOSE score. The STEPP analysis, in parallel with an understanding of the potential risks associated with both medical treatment and surgery, substantially improves the quality of information available to the clinician and patient in the clinical decision-making process around septoplasty.

Van Egmond *et al.*'s[58] 2019 study reached similar conclusions to those of the NAIROS in a trial of 203 participants randomised to receive either septoplasty, with or without turbinate surgery, or non-surgical management. Neither study found a relationship between outcomes and age or gender. The NAIROS reported a 14-point SNOT-22 surgical superiority score at 12 months, compared with 9.7 points in van Egmond's[58] study, although the latter's data transformation and variable medical arm treatments makes direct comparison difficult. Van Egmond *et al.*'s[58] subjective, categorical, clinician-rated assessment of baseline severity failed to correlate with outcome. The mild category comprised 30% of participants, but there is no evidence for the comparability of the subjective assessment with quantitative NOSE scores. In contrast, the NAIROS substantially enhances understanding of the role of quantitative patient-reported data in the selection of patients for surgery by demonstrating that the degree of improvement in symptoms is closely related to baseline severity stratification.

Discontinuation of allocated treatment

The NAIROS trial design did not allow for formal crossovers from one treatment arm to the other. The ITT analysis therefore risks accepting a null hypothesis if the non-surgical arm ultimately contains too many individuals who have undergone surgery, resulting in an underestimation of the treatment effect size.[160] Approximately 20% of participants in the trial did not receive the treatment to which they were allocated. Of 190 participants allocated to medical management, 46 (24%) subsequently had surgery. At 6 months' follow-up, only five patients had discontinued medical treatment and had undergone surgery, but, by the 12-month follow-up, a further 37 (30%) of the 125 retained participants had undergone surgery and completed SNOT-22 scores (see *Figure 7*). All but 12% of the septoplasty arm underwent surgery. Despite these groups discontinuing allocated treatment, the NAIROS ITT analysis found superior benefit from surgery, confirmed by per-treatment and per-protocol analyses (see *Figure 9*).

Secondary outcome measures

The benefits of septoplasty are also seen in the secondary outcome measures, including clinical airflow assessment, PROMs and objective measurements of PNIF and rhinospirometry.

Double Ordinal Airway Subjective Scale

The DOASS improved dramatically in the septoplasty arm at 6 months and 12 months. Absolute subjective DOASS, the subjective comparator of the worse versus the better nostril airflow, revealed a significant treatment-related shift from predominantly unilateral nasal airflow to equal airflow through both nostrils, which was more marked in magnitude in the surgical arm than in medical treatment arm at both 6 and 12 months (see *Figure 10*). As a simple clinical patient-reported outcome, the DOASS reflects the findings of previous studies,[161,162] showing the specific aerodynamic benefit of septoplasty. Therefore, it may be a useful tool to audit surgical outcomes, or indeed future trials of nasal airway surgery.

Nasal Obstruction Symptom Evaluation score

At baseline, continuous NOSE scores had a broad distribution, with a median score of 70 (IQR 60–82.5) in the surgical arm and 70 (IQR 60–85) in the medical arm (see *Table 7*). In concordance with van Egmond *et al.*,[58] the NOSE score in the NAIROS showed a consistently large effect in favour of septoplasty at 12 months. In North America in particular,[163] the NOSE is a widely used brief PROM, validated for septoplasty.[164] The NAIROS has shown the value of the NOSE as both a baseline severity measure and outcome measure, with global utility.

Subscales of the Sino-nasal Outcome Test-22 items

Results consistently show greater improvement in the surgical arm than in the medical treatment arm in scores across each of the four SNOT-22 domains (nasal, sleep, ear and emotional) (see *Figure 11*). Bugten *et al.*[165] found similar improvements in all four subscales in an uncontrolled study of septoplasty assessed at 6 and 12 months. The impact of septal surgery in improving the SNOT-22 scores is mirrored in other studies of snoring[166] and eustachian tube dysfunction.[167] The impact on sleep may be equally important to the participants' bed partners as it is to the participants themselves. Factors such as fatigue, emotional instability and mood are known to inflate SNOT-22 scores in tandem with nasal disease severity.[168] The SNOT-22 measures the spectrum of symptom improvement following septoplasty; however, the brevity of the NOSE, which also includes a sleep item, is a more practical tool in a busy clinical setting.

Objective airway assessment

UK ENT clinicians rarely offer objective airway assessment prior to surgery, which is currently predicated on their subjective clinical assessment. The NAIROS has demonstrated that an endoscopic assessment of the nasal airway, augmented by baseline NOSE score, predicts the degree of symptomatic improvement following surgery for nasal obstruction. Objective airway assessment was requested in the NIHR HTA programme commissioning brief and the NAIROS has offered a unique opportunity to assess any added value from two of the most commonly reported nasal airway assessment measures.

The COVID-19 pandemic had a considerable impact on NAIROS data acquisition, particularly clinical nasal examination, the DOASS and objective airway assessments, which were not permitted after March 2020.

Peak nasal inspiratory flow rates at 6 and 12 months demonstrated a marginally greater improvement in the septoplasty arm than in the medical management arm (see *Figure 13*). Similar results have also been identified in other studies.[57,58,166] PNIF has been recommended as a simple, reliable and reproducible test of nasal airway patency.[169,170] However, studies to date have not shown good correlation between PNIF and patient-reported outcomes in nasal conditions,[171,172] and PNIF does not provide information on participants' individual nostril airflow, which is of particular relevance in assessing septoplasty outcomes.

Rhinospirometric measurements of the absolute MIV results after septoplasty (see *Figure 14*) demonstrate a significant improvement towards equal airflow through each nostril in comparison with medical management, aligning with the patients' DOASS scores. The tidal breathing assessment shows similar improvements (see *Figure 15*). Notably, there was no evidence of negative impact on the better breathing nostril as a result of surgery. The statistical direction of effect still favours septoplasty at 12 months, but neither MIV nor tidal breathing were significantly different between the two arms at 12 months (see *Table 8*); this is most likely owing to the much smaller sample size and the effect of 25% of medical management participants withdrawing to have non-trial surgery.

What is the relationship of subjective and objective measures?

Aziz *et al.*'s[173] systematic review found objective assessment tools for diagnosing nasal septal deviation to be of limited use if used in isolation, lacking sensitivity and specificity compared with clinician nasal examination. However, Boyce *et al.*,[56] using rhinospirometry as a gold standard, reported that the patient-reported DOASS had a sensitivity of 100% and specificity of 60% when assessing 46 patients with a deviated nasal septum. Unlike some objective assessments of the nasal airway, the DOASS can provide discriminatory airflow information on both nostrils, even in the presence of complete unilateral nasal obstruction.

The NAIROS assessed the relationship between the DOASS and the NPR in all 307 participants who attended for baseline assessments. A correlation of $p = 0.77$ was demonstrated between the DOASS and MIV (see *Appendix 1*, *Figure 29*) and a further correlation of $p = 0.78$ between the DOASS and tidal breathing (see *Appendix 1*, *Figure 30*), indicating a strong correlation between subjective and objective airflow measurements. This suggests that the DOASS can provide useful airflow assessment in lieu of objective assessments such as rhinospirometry, which is expensive, cumbersome and operator dependent.

To test the relationship between the primary outcome and airflow measurements, the NAIROS analysed SNOT-22 outcomes in relation to baseline severity stratification with post-decongestant DOASS (see *Appendix 1*, *Figure 32*). The NAIROS did not find a clinically useful relationship to facilitate the use of the DOASS to predict postoperative symptom (PROM) improvement following surgery, although this was a post-decongestion measurement, thus not necessarily reflecting normal nasal airflow.

In summary, objective measures of nasal airflow show greater nasal airway improvements across the range of baseline severity in the septoplasty arm than in the medical management arm. Rhinospirometry and the DOASS appear to demonstrate greater utility than PNIF as objective assessments. However, the use of the NOSE in combination with clinical examination offers a robust, reliable and inexpensive assessment for surgical decision-making.

Reduction of the inferior turbinate

The NAIROS protocol permitted turbinate reduction, reflecting UK surgical practice. Of the 155 septoplasties for which information on turbinate reduction was available, 88 (57%) included a turbinate reduction.

There was considerable variation across trial sites on the frequency of turbinate reduction performance. The intention had been to perform a stratified analysis by turbinate reduction, but, given that there was considerable variance between the intention to reduce the turbinate at baseline and actual turbinate reduction at the time of surgery, this was not particularly informative (see *Appendix 1*, *Table 57*). At baseline, those in the surgical arm who were recommended for turbinate reduction had slightly higher SNOT-22 scores.

The outputs of the NAIROS infer that turbinate surgery added no additional improvement to septoplasty alone (see *Table 10*). However, the decision to perform turbinate reduction was at the discretion of the investigator and, had this additional procedure not taken place, the improvements noted may not have been evident. Van Egmond *et al.*[58] similarly reported no additional benefit of turbinate surgery. The evidence for turbinate surgery in the literature is conflicting. Van Egmond *et al.*'s[61] 2018 systematic review concluded that 'the limited number of studies comparing septoplasty with concurrent turbinate surgery to septoplasty alone generally showed postoperative improvement, but their results should be interpreted with caution due to methodological "flaws" '. The trial does not address the question of whether or not turbinate surgery is more beneficial in improving the nasal airway than septoplasty alone.

Treatment success

The NAIROS specifically asked participants who received septoplasty about success of treatment (see *Table 9*). At 6 months, 134 out of 166 participants in the septoplasty ITT arm provided information on their perception of nasal airway improvement (i.e. better/same/worse): 108 out of 134 (80.5%) felt that their nasal breathing had improved, 19 (14.1%) considered their nasal breathing to be the same and seven (5.2%) reported that it had deteriorated. At 12 months, fewer data were available, with only 89 out of 166 participants providing information. Of those, 66 out of 89 (74.2%) participants felt that their nasal breathing was better and eight (8.9%) believed it was worse. Van Egmond *et al.*[58] reported that subjective and objective benefits of septoplasty persisted over the full 24 months of follow-up, although they did not expressly report patient satisfaction rates. In contrast, Pedersen *et al.*,[158] published an assessment of patient-reported satisfaction at 12 months using a subjective, categorical, patient-rated assessment of severity. They reported no improvement in 69% of patients with mild nasal obstruction and in 43% of patients with moderate nasal obstruction before surgery. In addition, 15% of all patients in the study by Pedersen *et al.* reported severe nasal obstruction 12 months after surgery. Neither study accurately quantified mild symptoms. Overall, the NAIROS participant perception of improvement in their nasal airway appears favourable, compared with other studies, potentially because patients with mild baseline scores were excluded. Our qualitative work reported that septoplasty had varying levels of success among the participants sampled. However, those who found the operation effective typically experienced quite high levels of success, with participants feeling that they had experienced a major reduction in their symptoms following the operation. Studies reporting success of septoplasty demonstrate considerable heterogeneity[21,174] in the manner of assessment, making direct comparisons difficult.

Only 6 out of 166 surgical arm participants (3.6%) were recommended to consider revision septoplasty, although the reasons underpinning these decisions were not recorded. For four participants, the decision to offer revision surgery was reported for either 'same' or 'worse' symptoms. For the remaining two participants, symptoms were reported as 'better'. In the only other RCT of septoplasty with or without turbinate surgery,[58] 1% of patients required revision septoplasty. Reported rates in the literature vary from 1% to 12%.[175–177]

In all NAIROS cases, surgery was performed by experienced surgeons in both teaching and district hospital otolaryngology departments. The results of both the NAIROS and van Egmond *et al.*[58] provide a benchmark for colleagues and trainees in the wider surgical community to assess nasal airway surgery outcomes in their own practices.

Safety

Adverse events/serious adverse events

None of the 227 AEs or 23 SAEs related to treatment was deemed to be life-threatening. *Appendix 1*, *Tables 63* and *67*, and *Table 11* highlight the categories and causes of AEs.

Overall, complication rates on initial assessment appear higher in comparison with published series, but several factors are noteworthy. First, the regular scrutiny of participants in a trial setting is greater than in standard NHS practice. Second, the trial-specific questioning regarding a potential complication may invite a positive response, in contrast to standard practice where no specific enquiry is made. Third, the mandatory postoperative endoscopic trial assessment would identify asymptomatic adhesions or perforations that typically go unnoticed in standard practice.

Some degree of mild bleeding is expected after nasal surgery. The NAIROS reports seven participants (4%) requiring re-admission to hospital with nasal bleeding, all of whom had septoplasty with inferior turbinate reduction. In a review of postoperative complications following septoplasty with or without turbinate reduction in 5639 patients, Dąbrowska-Bień *et al.*[66] reported a postoperative bleeding rate of 3.3% overall (without/with turbinate reduction: 2.6%/4.1%). However, the heterogeneity of inclusion criteria and treatment of the bleeding group were unclear. In anticipation of the potential for postoperative bleeding, the NAIROS protocol stipulated nasal septal suture closure, rather than the often-used alternative of nasal packing. Avoidance of nasal packing also facilitated day-care treatment. In a systematic review, Wang *et al.*[178] noted that postoperative pain, headache and adhesions were significantly lower in the transseptal suturing group than in the nasal-packing group. Nasal packing and transseptal suturing appear to be equivalent regarding postoperative bleeding, septal perforation and infection rates.

Postoperative infection following nasal surgery covers a broad range of conditions, from that of increasing nasal discomfort assumed to be secondary to infection, through to obvious postoperative cellulitis or inflammation that may be more severe and even require hospitalisation. Van Egmond *et al.*[58] reported a 7% postoperative infection rate, lower than the NAIROS (12%). In a review of 10 studies, Kullar *et al.*[179] noted that perioperative/postoperative antibiotics did not reduce the incidence of infection following septorhinoplasty.

We noted a higher incidence of participants reporting a reduction in sense of smell following surgery (11%) than in other studies,[66] but about equal to that of the 2019 Swedish National Register study.[158] A closer analysis of the NAIROS outcomes was conducted in relation to this issue. We cross-referenced participants' responses to loss of smell (see *Appendix 1*, *Table 66*) at 6 and 12 months with the SNOT-22 question regarding 'loss of sense of smell or taste'. Only four participants (3%) reported a worsening of sense of smell between baseline and 6 or 12 months in response to both assessments. Smell perception is recognised as being highly subjective,[180] and is difficult to characterise without using specific psychophysical tests.

In a study of 100 septoplasty patients undergoing standardised preoperative and postoperative photography, Vuyk *et al.*[181] noted significant postoperative nasal aesthetic changes in 1% of patients, with minor changes in > 20% of patients. Other studies report cosmetic changes in between 0.4% and 7% of patients.[66,158] The NAIROS identified 17 participants at 6 or 12 months (10%) who noted a change in the appearance of their nose. It is important to note that judging subtle changes in nasal appearance without photographic records is highly subjective and, furthermore, any postoperative cosmetic change may be considered beneficial, as opposed to detrimental. The NAIROS did not quantify this further.

Dental or palatal numbness is also a recognised AE following septal surgery. In a series of 107 septoplasty patients, Chandra *et al.*[182] noted a prevalence of 2.8% of such numbness. The NAIROS noted 18 participants (11%) with this complaint at 6 or 12 months.

Overall, more complications were reported at 6 months than at 12 months, although, at 12 months, COVID-19 restrictions had led to a cessation of clinical nasal assessments.

Perforations were found in the nasal septum of 6 out of 179 (3%) NAIROS participants at 6 or 12 months. Other studies quote similar rates: Dąbrowska-Bień *et al.*[66] found perforations in 2.3%, Pederson *et al.*[183] found perforations in 2% and van Egmond *et al.* found perforations in 2% of patients.[58] Adhesions (scarring) between the nasal septum and side walls of the nose were noted in 7 out of 179 (4%) participants at 6 or 12 months. Adhesions, many of which are asymptomatic, have been noted in up to 36% of patients in a review of retrospective studies.[184] All NAIROS participants underwent postoperative nasal endoscopy, a level of scrutiny that is not routine in clinical practice and is likely to have identified participants with small nasal septal perforations and adhesions that are commonly asymptomatic findings.

Economic evaluation

On average, septoplasty was more costly and more effective in terms of improvements in SNOT-22 scores and QALYs gained. When AEs were used as the outcome measure, septoplasty, a surgical intervention, incurred a greater number, as expected.

The incremental cost per QALY gained at 12 months was £27,114. The probability of septoplasty, with or without turbinate surgery, being cost-effective, compared with medical management, was 15% at a £20,000 threshold for an additional QALY, and 68% at a £30,000 threshold. Using strict NICE guidance, septoplasty, with or without turbinate surgery, has a low probability of being considered cost-effective at 12 months. A sensitivity analysis estimating the cost of surgery using microcosting, instead of the NHS tariff, suggested that septoplasty had a 79% probability of being considered cost-effective at 12 months at a £20,000 threshold for an additional QALY. This result provides further support that it is the cost of surgery determining cost-effectiveness at 12 months. However, these results need to be interpreted with caution.

It was anticipated that septoplasty was likely to be more costly and potentially more effective, but the 12-month duration of the trial was insufficient for the additional benefit to offset the additional costs of surgery. This is illustrated in the economic analyses in which we compare the incremental cost per QALY for septoplasty versus medical management at 6 months' follow-up (> £100,000) with that at 12 months (£27,114). For this reason, an economic model was undertaken to extrapolate the trial results to 24 and 36 months post randomisation. The model was a simple decision-tree populated using the trial data and clinical inputs. At 24 months, septoplasty remained, on average, more costly and more effective in terms of QALYs gained; however, the ICER reduced to around £13,000, which is well within the £20,000 NICE threshold for an additional QALY. By 36 months, the septoplasty ICER had reduced to around £7000 per QALY. In these analyses, septoplasty had the highest probability of being considered cost-effective, compared with medical management, at 24 months (99%) and 36 months (100%), at a £20,000 threshold for an additional QALY.

This is the first RCT to evaluate the cost-effectiveness of septoplasty, compared with a standardised medical management regime, in the management of a deviated nasal septum.

Strengths and limitations

Study strengths

- To our knowledge, the NAIROS is the first RCT of septoplasty, with or without turbinate surgery, incorporating two well-defined, reproducible treatment arms.
- The trial was designed to have 90% power to detect the MCID of 9 units on the SNOT-22 scale. The trial recruited to target and the observed attrition level was no higher than allowed for in the sample size calculations.

- The primary outcome is patient-reported, and a major strength of the trial is that we amended the protocol to collect this remotely by e-mail, post and an online platform. This helped to maximise data accrual, especially during the later period of the trial when face-to-face visits were halted owing to COVID-19.
- We recruited participants from a wide range of sites across Great Britain, which included both large teaching hospitals and smaller district general hospitals, to represent the whole population.
- A broad range of well-recognised, validated outcome measures, both subjective and objective, were used to determine the success of treatment among the trial participants. The trial recruited to target with no funding extension.
- An electronic version of the primary outcome PROM was successfully used to achieve the target number of participants reporting and returning the associated data.
- We conducted the primary statistical analysis on the complete-case data. A sensitivity analysis accounted for the small number of withdrawals from the trial and missing data using multiple imputation. The additional analyses undertaken supported the primary ITT analysis conclusions. The per-protocol and per-treatment analyses corroborate the ITT results, confirming the greater improvement in patient-reported outcomes of those participants receiving surgery than those treated medically.
- The objective measures of nasal airflow, specified by the funder, confirmed the impact of surgery over medical management, although these did not contribute over and above PROMs in determining the best management strategy for patients with a deviated nasal septum.
- A major strength of this trial was the embedded economic evaluation. The response rate to the data collection tools used to inform the economic analysis was relatively high, with nearly two-thirds of participants having complete data. Costs and effects were estimated at 12 months and were extrapolated so that the longer-term costs and benefits associated with septoplasty could be considered. Finally, a number of sensitivity analyses were undertaken to test the robustness of the economic conclusions. Reassuringly, these analyses did not change our conclusions, in that septoplasty was, on average, more costly but more effective than medical management. An adjusted analysis using SUR was used to estimate the difference in costs and QALYs. This is a robust method for estimating the ICER as it facilitates the simultaneous estimation of costs and effects and takes into consideration unobserved individual characteristics that may affect costs and effects.[114]
- The inclusion of a qualitative process evaluation enabled a comprehensive understanding of the benefits and burdens of both treatments and highlighted ways in which treatments could be optimised. It also ensured that learning from the trial is captured to inform future surgical trials.
- Patients were influential voices throughout the evolution of the NAIROS RCT, from PPI at the design outset to ongoing contributions from the lay participant on the TSC.

Study limitations

- All patients who were sent a PIS were entered on the screening log. Pre-screening patient telephone contact and dedicated NAIROS clinics were not permitted by the NHS REC. As a result, it is likely that only those motivated patients identified in GP referral letters/busy ENT clinics, and who were prepared to return for NAIROS assessments, were recruited and took part in the randomisation process.
- The NAIROS consent process was complex and time-consuming, incorporating three stages. The first two stages of consent (eligibility and audio-recordings) could be completed by a research nurse, thereby saving time in a busy clinical environment. However, given that the trial was a CTIMP, stage 3, the consent to the main trial, required a clinician. The consent process and the trial assessments took at least 1–2 hours, limiting the number of patients recruited in each clinic.
- Although it was recommended that recruitment take place in research clinics, many sites were unable to do so, which led to challenges in finding both time and physical space for recruitment at some sites.
- At baseline > 80% of patients had NOSE scores in the severe/extreme category. It is likely that some patients with less severe nasal obstruction either responded to treatment provided in primary care or, once referred, did not wish to participate in the trial.

- The qualitative substudy interviewed only one person who declined to participate in the trial. We therefore know relatively little about the preferences and experiences of those who did not wish to participate in the trial.
- Nasal obstruction is a non-specific symptom with many underlying possibilities (e.g. allergic rhinitis, non-allergic rhinitis, nasal valve dysfunction). In addition, making a diagnosis of septal deviation is challenging in primary care because of the limitations of nasal examination without specialist equipment.
- The NAIROS surgical interventions were performed by experienced surgeons. In NHS practice, septoplasty with or without turbinate reduction is frequently performed by junior trainee surgeons, albeit often supervised by more senior colleagues.
- COVID-19 had a significant impact on the NAIROS trial. All forms of airway clinical assessment and objective testing of nasal airway function were suspended from March 2020 onwards. As a result of the smaller numbers of participants assessed at 12 months, this may have had an impact on the precision of the statistical outputs.
- Twelve months is too short a time horizon for the costs associated with a surgical intervention such as septoplasty to be offset by the benefits; however, surgery becomes cost-effective within 24 months.
- One of the main challenges of the economic evaluation was the microcosting exercise. First, the NHS tariff includes additional costs such as overheads that were not included in the microcosting exercise. Second, costs were sourced from only one site, but are presented for the reader to judge generalisability. Finally, septoplasty data used to inform the microcosting exercise were collected only for participants randomised to septoplasty, but 30% (n = 47) of participants randomised to medical management underwent septoplasty. This has meant that variations in surgical costs were not captured in the bootstrapping analysis as every participant who underwent surgery was assigned the same cost.
- The economic model was populated using data from a single study. However, validity checks and sensitivity analyses were undertaken to ensure the robustness of these results.

Generalisability

The challenges faced in the design, implementation and analysis of surgical RCTs are well recognised.[129,185]

Our qualitative work showed that the trial design was considered positively. Clinicians considered normal clinical practice as being reflected by a trial of medical therapy before offering surgery. Patients considered the option of deferred surgery, if randomised to the medical management arm, as a key factor in deciding to participate in the main trial.

Nasal obstruction is the most common nasal symptom presentation in secondary care. The NAIROS excluded those with nasal bone deviation, as stipulated in the commissioning brief. The selection criteria were unable to exclude those with concomitant allergic or non-allergic rhinitis. The NAIROS participants may have had both nasal structural and mucosal disease, for which current standard NHS care may involve both septoplasty and nasal steroid spray in combination, whereas trial participants were offered only a single treatment category.

One investigator in the qualitative study noted that there may be unwillingness of colleagues to refer the most severely deviated nasal septum patients for recruitment, in the belief that severe deviation at the front of the nostril will respond to surgical treatment only. Notably, this concern was not raised by other investigators and the NAIROS recruited patients with a broad range of NOSE score severities.

There is a dichotomy of potential treatment duration in the two trial arms as it relates to the ‘real world’. After an initial perioperative symptom exacerbation, a successful septoplasty produces a permanent change in the nasal airway and symptomatic improvement is expected to be long-lasting. In contrast, nasal steroid sprays require potentially unlimited duration of treatment, with possible side effects, as well as a willingness of patients to comply with and pay for treatment.

We had intended, during the course of the NAIROS, to compare the main trial 'acceptors' and 'decliners' to gather information on the generalisability of the trial cohort to the total population of those referred for consideration of surgery. However, this was not practical given the small number of 'decliners' in the cohort recorded on the screening logs. There were several reasons for this. First, the difficulty in defining eligible recruits, alluded to previously. In addition, the NHS REC stipulated that telephone pre-screening of patients was not permitted. As a result, some patients seen for assessment did not have a deviated septum. In most sites, participants who were sent a PIS, attended clinic and were found to be eligible were subsequently recruited, and only 45 participants who consented to eligibility screening, but not to the main trial, had data available for analysis.

The potential applicability of the NAIROS outcomes across different ethnic groups should be tested further.

Variations in surgical technique can affect the generalisability of surgical RCT findings.[185,186] The NAIROS minimised variability in surgical technique by standardising critical parts of the procedure (closed approach, site of incision, closure) and postoperative care undertaken. However, surgeons were allowed to adopt a variety of techniques to manipulate the cartilage skeleton into place, and so overall its results reflect the generality of current surgical practice.

Implications for practitioners and health services

There are currently no evidence-based guidelines for the definitive treatment of nasal obstruction in the presence of a deviated nasal septum. In the UK many existing Clinical Commissioning Groups require up to 6 months of nasal steroid treatment in primary care before sanctioning referral to secondary care ENT services.[153,154] A 2015 US-based clinical consensus statement[187] agreed a 'trial of medical therapy of more than 4 weeks' duration is unnecessary to assess surgical candidacy for septoplasty. However, the panel did not reach consensus on the statement that a four-week trial of nasal steroid prior to septoplasty is sufficient to assess surgical candidacy'.

Given that approximately 16,000 septoplasties are undertaken annually in the NHS, the NAIROS results justify the research investment made, despite its hitherto limited evidence base.

The NAIROS is the first RCT that definitively demonstrates that septoplasty, with or without turbinate reduction, in comparison with a medically treated cohort, is a highly effective procedure with evidence that it may be considered cost-effective at 24 months. The NAIROS-generated evidence confirms that the use of a brief assessment tool (the NOSE) in combination with endoscopic assessment/confirmation of a deviated nasal septum as the principal pathology defines those patients who will have benefit from septoplasty, with or without turbinate reduction. Although objective measurements have corroborated the superiority of surgery over medical management, the NAIROS has not demonstrated that such measurements provide useful information beyond that of clinical and baseline PROM assessment.

Most patients will have sought treatment in community and primary care settings and will have had a trial of nasal steroid spray. We recommend that patients who do not see improvement with this first-line treatment are referred to secondary care to undergo a clinical nasal airway assessment and complete the NOSE severity scale. When weighing up the risks and benefits of different treatment strategies, those with a NOSE score of > 30 can reliably be advised that septoplasty, with or without turbinate surgery, is a highly effective, evidence-based treatment option and that the level of predicted benefit will relate to the severity of their symptom burden at presentation.

Context of trial/informing NHS guidance

The NAIROS has shown that baseline assessment using the NOSE scale can predict the degree of postoperative symptom improvement. In this regard, we have operationalised the NOSE score and would recommend its use in standard clinical practice for preoperative decision-making for nasal septal surgery.

Modest overall improvements in SNOT-22 scores in the medical management arm were evident at both follow-up intervals. The reasons for this improvement, beyond the initial 6-month trial period of steroids/saline spray, are likely to be related to several factors. First, as previously described, around 25% of the medical management arm underwent septoplasty during the trial. Second, it is recognised that rhinitis has a fluctuating impact on nasal symptoms and this may have potentially contributed to the improvement effect noted. Nasal steroids/saline improve congestion and nasal airflow among patients with allergic and non-allergic rhinitis.[75,188,189] It is expected that a proportion of participants should obtain some benefit from this treatment given the prevalence of rhinitis in the general population.[190] Existing guidelines[187] indicate that there is no consensus among clinicians as to the benefit of medical management (in comparison with surgery) as a treatment for patients with a deviated nasal septum. The most common reasons cited for ceasing medical treatment in the NAIROS were 'not happy with sprays/side effects' (78%) and worsening symptoms (15%). Pragmatically, nasal spray delivery may be impeded or impossible in cases of a particularly deviated septum. In practice, treatment discussions with patients wishing to consider medical management should also include reference to the potential risks of side effects including minor nosebleeds, nasal dryness and irritation, and the need for long-term treatment and associated costs.

The majority of patients presenting to primary care with nasal obstruction (and without red-flag symptoms) who do not have a deviated nasal septum may be treated medically. Those whose symptoms persist despite treatment should be referred to secondary care for a thorough and careful clinical assessment, including nasal endoscopy and NOSE score assessment. The NAIROS has demonstrated from both clinical and health-effectiveness perspectives that, for those patients with a NOSE score of > 30 and a deviated nasal septum, septoplasty, with or without turbinate reduction, is superior to long-term medical therapy.

Implications for patients and the public

Ultimately, it is for the patient to decide based on the information provided whether, after weighing up risks and benefits, they wish to consider medical therapy or to proceed with surgery.

The NAIROS has developed evidence showing that septoplasty, with or without turbinate reduction, outperforms a combination of nasal steroid/saline sprays in the treatment of nasal obstruction associated with a deviated nasal septum. Given the heterogeneity of patients who present with nasal blockage, an initial trial of medical management remains appropriate for most patients. The duration of this treatment is not yet defined.

After a trial in the primary care setting of nasal steroid/saline medication, those patients referred to secondary care who have endoscopic evidence of septal deflection in the presence of moderate, severe or extreme NOSE scores, when weighing up the risks and benefits of different treatment strategies, can reliably be advised that septoplasty, with or without turbinate surgery, is a highly effective, evidence-based treatment option, and that the level of predicted benefit will relate to the severity of their symptom burden at presentation.

Implications for research

- The most important research priority to emerge from the NAIROS trial is the requirement for a patient decision aid to explore management of a deviated nasal septum. Surgery is more clinically effective, but carries a greater risk of AEs. Medical management carries fewer risks, but results in ongoing costs. A decision support tool would allow a patient to discuss their own individual health risks, along with their values and preferences, at the time of referral, and to integrate these with the NAIROS outputs, which can also be used to enhance and update currently available patient information resources.

- We recommend that a meta-analysis of outcomes with van Egmond *et al.*'s[58] RCT be conducted to analyse the pooled data and reach objective conclusions on the clinical effectiveness and cost-effectiveness of septoplasty in the short and long term based on the strengths and limitations of both RCTs.
- Further studies are required to assess the optimum medical treatment and its duration in the management of nasal obstruction associated with a deviated septum.
- Further work to determine the use of the DOASS as a discriminatory tool with possible utility in primary care.

Chapter 8 Conclusions

Septoplasty, with or without turbinate reduction, is a clinically effective intervention. Participants with a deviated nasal septum with a moderate, severe or extreme baseline severity of nasal obstruction symptoms had an improvement in patient-reported outcomes at 6 and 12 months. This improvement surpassed that of standardised medical management. A sensitivity subanalysis confirmed that surgery is increasingly effective with increasing baseline symptom severity. Improvements were correspondingly noted in both participants' perception of nasal airflow and objective measures of nasal function.

The NAIROS-generated evidence confirms that a NOSE score of > 30 in association with a symptomatic deviated nasal septum determines which patients will benefit from septoplasty, with or without turbinate reduction.

Septoplasty, with or without turbinate reduction, is more costly and effective than medical management. The results suggest that surgery has a low probability of being cost-effective at 12 months but may be considered cost-effective at 24 months.

The findings of the qualitative substudy were consistent with an improved outcome in the surgical treatment arm, but demonstrated that, on an individual level, there were still patients who did not report benefit from surgery and others who did experience useful symptom improvement with medical management. Additional information might enable medical treatment to be optimised and improve the patient experience of surgery, particularly in the postoperative period. Surgeons reported that they would ideally like to be able to identify in advance which patients were most likely to benefit from surgery, but there were mixed views about the use of standardised outcome measures as part of decision-making.

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Data-sharing statement

The final anonymised data set from this trial will be available to the scientific community via an online data repository, subject to regulatory and ethics approval. Requests for data should be directed to the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Additional statistical analysis

TABLE 25 Treatment allocation by stratification factors for the ITT population only (*n* = 307)

Stratification factor	Trial arm, *n* (%)		Total (*N* = 307), *n* (%)
	Septoplasty (*N* = 152)	Medical management (*N* = 155)	
Moderate male	11 (7)	15 (10)	26 (8)
Moderate female	7 (5)	7 (5)	14 (5)
Severe male	54 (36)	53 (34)	107 (35)
Severe female	23 (15)	27 (17)	50 (16)
Extreme male	35 (23)	31 (20)	66 (22)
Extreme female	22 (14)	22 (14)	44 (14)
Total	152 (100)	155 (100)	307 (100)

TABLE 26 Site recruitment activity (descending order)

Site number	Site	Date opened	Date last participant recruited	Recruitment duration (weeks)	Number recruited
01	Newcastle	18 January 2018	23 September 2019	87.6	76
08	Aberdeen	31 January 2018	16 July 2019	75.9	37
14	Aintree	12 June 2018	5 November 2019	73.0	27
15	Leeds	5 April 2018	5 December 2019	87.0	27
02	Great Yarmouth	14 March 2018	28 August 2019	76.0	22
07	Dundee	23 January 2018	15 October 2019	90.0	20
09	Stockport	10 April 2018	30 September 2019	76.9	20
16	Lanarkshire	5 July 2018	14 November 2019	71.0	20
04	Wigan	14 March 2018	5 November 2019	85.9	18
03	Bradford	25 May 2018	19 November 2019	77.6	17
06	Plymouth	24 April 2018	29 October 2019	79.0	17
17	Salisbury	9 April 2018	25 November 2019	85.0	17
10	London	28 February 2019	13 November 2019	36.9	14
11	Newport	17 May 2018	9 October 2019	72.9	13
12	Birmingham	23 March 2018	3 September 2019	75.6	13
13	Carlisle	1 May 2018	19 September 2019	72.3	11
05	Darlington	23 April 2018	24 June 2019	61.0	9
Total		18 January 2018	5 December 2019	98.0	378

TABLE 27 Weeks from randomisation to withdrawal from trial

	Septoplasty arm (*n* = 188)	Medical management arm (*n* = 190)	Overall (*n* = 378)
Withdrew, *n* (%)	20 (11)	26 (14)	46 (12)
Time in weeks from randomisation to withdrawal			
Median (IQR)	24 (14–33)	31 (18–50)	27 (18–48)
Range (minimum, maximum)	(0, 65)	(0, 68)	(0, 68)

TABLE 28 Line listing of reasons for withdrawal from the trial (*n* = 46)

Trial arm	Time from randomisation to withdrawing (weeks)	Reason did not complete the trial as randomised	More information of reasons for withdrawing from the trial
Septoplasty	0	Other	Changed mind
Septoplasty	5	Other	Patient unable to stay overnight
Septoplasty	7	Other	Patient no longer wanted surgery
Septoplasty	8	Other	Patient had another surgery booked so cancelled her nasal surgery
Septoplasty	10	No reason given by participant	
Septoplasty	18	No reason given by participant	
Septoplasty	21	Protocol deviation	Sponsor advised that the patient would need to be withdrawn as they missed the deadline for surgery as stated in protocol
Septoplasty	21	Participant lost interest in the trial	Patient has lots of other legal issues with another specialty and she feels she does not want to take up any more of the NHS time. Nothing to do with the NAIROS
Septoplasty	23	Other	After further reflection did not want surgery after being randomised to surgery
Septoplasty	24	Other	Trial site requested withdrawal because septoplasty was being performed after the 8-week window, as the patient cancelled the first surgery date
Septoplasty	26	Other	Symptoms had resolved after surgery, so the participant did not want to complete any more follow-up
Septoplasty	27	Other	Unable to contact patient
Septoplasty	28	Other	Does not want any more surgery and nasal symptoms have improved by themselves
Septoplasty	30	No reason given by participant	
Septoplasty	32	Participant has other duties (e.g. caring)	Patient finished university education in Plymouth and relocated to Cornwall. It was not convenient for him to come back for surgery because of his new life commitments
Septoplasty	34	Participant lost interest in the trial	

TABLE 28 Line listing of reasons for withdrawal from the trial (n = 46) (*continued*)

Trial arm	Time from randomisation to withdrawing (weeks)	Reason did not complete the trial as randomised	More information of reasons for withdrawing from the trial
Septoplasty	51	Other	Work commitments make it difficult to meet the trial timelines
Septoplasty	52	No reason given by participant	Participant contacted clinic to cancel her 12-month appointment on 28 October 2019 stating she does not want any further appointments
Septoplasty	52	Participant has other duties (e.g. caring)	
Septoplasty	66	Other	Patient complained about all the questionnaires, and even after having surgery, she is no better off and wants nothing further to do with the trial
Medical Management	0	Other	Patient completed full-screen appointment, prescription taken to pharmacy; however, changed his mind
Medical Management	0	Other	Patient was randomised to medical management but he wanted surgery; therefore, he withdrew from the trial
Medical Management	0	Participant lost interest in the trial	
Medical Management	2	Other	Unable to wait for prescription at pharmacy on day. Not been back to collect prescription as not had time. Does not want to continue in trial
Medical Management	9	Other	Did not feel that the medical management arm was effective in treating his nasal issue
Medical Management	10	Other	Kept forgetting to take the nasal sprays and did not feel it was making any difference
Medical Management	18	Participant has other duties (e.g. caring)	Participant discovered she had other health issues unrelated to the trial and had to focus on those
Medical Management	21	Other	Patient wrote on form 'Condition resolved through change of diet, loss of weight and increased exercise'
Medical Management	24	Participant lost interest in the trial	Patient did not attend for 6-month follow-up appointment. Several attempts made to contact; when finally spoke on the telephone, patient stated he had stopped taking medication approximately 2 months ago, did not really feel any benefit so did not contact us
Medical Management	25	Other	Patient feels that steroid spray or nasal surgery would not improve her current symptoms
Medical Management	28	Other	Patient wanted surgery
Medical Management	29	Other	Patient is undergoing other medical investigations. Becoming quite muddled with hospital appointments and purpose of NAIROS trial
Medical Management	30	Other	Patient wanted surgery, not feeling any benefit
Medical Management	32	Participant lost interest in the trial	

continued

TABLE 28 Line listing of reasons for withdrawal from the trial (*n* = 46) (*continued*)

Trial arm	Time from randomisation to withdrawing (weeks)	Reason did not complete the trial as randomised	More information of reasons for withdrawing from the trial
Medical Management	39	Participant has other duties (e.g. caring)	
Medical Management	45	Participant lost interest in the trial	Participant only completed 6-month SNOT-22 remotely and he finally withdrew himself at 12 months
Medical Management	47	Participant lost interest in the trial	
Medical Management	48	No reason given by participant	
Medical Management	48	Participant lost interest in the trial	Was randomised to medical management, which provided no relief of symptoms. Is waiting for surgery and feels she is wasting her time coming back for another NAIROS appointment
Medical Management	51	No reason given by participant	He stated that he did not want to be involved in the trial; no reason given
Medical Management	51	Participant lost interest in the trial	Patient unhappy with surgical outcome
Medical Management	53	No reason given by participant	
Medical Management	54	Other	Participant declined any further trial activity
Medical Management	54	Participant lost interest in the trial	Declined to attend 12-month review. Agreed to complete questionnaires by post, but has failed to return them
Medical Management	61	Other	Patient did not attend several 12-month visit appointments and then contacted the PI's secretary to say that he no longer wished to be followed up by ENT. Has also not returned 12-month questionnaires even though has had three reminders
Medical Management	68	Other	Unable to attend because of his current job circumstances

TABLE 29 Summary of reasons for discontinuing allocated treatment (septoplasty arm)

Reason discontinued septoplasty	Frequency
Fear of surgery	1
No time to commit to surgery	3
Advised against surgery	1
Change of mind	9
Symptoms resolved	3
Other reason	6
Total	23

TABLE 30 Reasons for discontinuation of treatment for participants randomised to septoplasty (*n* = 16)

Fear of surgery	No time to commit to surgery	Advised against surgery	Change of mind	Symptoms resolved	Other reason	Other reason text
No	No	No	Yes	No	No	NA
No	Yes	No	No	No	No	NA
No	No	No	Yes	No	No	NA
No	No	Yes	Yes	Yes	No	NA
					Yes	Patient attended for operation; however, was unable to stay overnight so he did not have the operation
No	No	No	Yes	No	No	NA
No	No	No	Yes	No	No	NA
No	No	No	Yes	Yes	Yes	Following cardiology investigations as well
No	No	No	Yes	No	No	NA
No	No	No	No	No	Yes	Wanted to postpone surgery until end of May 2019 so they could continue to play rugby
No	Yes	No	No	No	No	NA
Yes	Yes	No	Yes	Yes	No	NA
No	No	No	Yes	No	No	NA
					Yes	Not happy with results of septoplasty; wants medical management
					Yes	Unable to contact patient; therefore, do not know the reason
					Yes	Owing to capacity issues (oncology and COVID-19), unable to see [participant] in study time frame

NA, not applicable.

TABLE 31 Summary of reasons for discontinuing allocated treatment (medical management arm)

Reason discontinued medical management	Frequency	Recategorised frequencies
Concerns about time	2	2
Side effects of spray	10	11
Unhappy with spray	36	65
Worse symptoms	15	15
Other reason	35	5
Total	98	98

TABLE 32 Reasons for discontinuation of treatment for participants randomised to medical management (*n* = 71)

Concerns about time	Side effects of spray	Unhappy with spray	Worse symptoms	Other reason	Other reason text	Recategorisation of 'other'
No	No	Yes	No	No	NA	
No	No	No	No	Yes	Was not interested in taking part	
No	No	No	No	Yes	Steroids not felt to be effective	Unhappy with sprays
No	Yes	Yes	No	No	NA	
No	Yes	No	Yes	Yes	Did not help the symptoms, felt it was not helping	Unhappy with sprays
Yes	No	Yes	No	No	NA	
No	No	No	No	Yes	Finished at 6-month point to request surgery	
No	No	Yes	Yes	No	NA	
No	No	Yes	Yes	No	NA	
No	No	No	No	Yes	Nasal blockage; requires surgery	Unhappy with sprays
No	Yes	Yes	Yes	No	NA	
No	Yes	Yes	No	Yes	Does not want to be using nasal sprays long term	Unhappy with sprays
No	No	No	No	Yes	Needed surgery	Unhappy with sprays
No	No	Yes	No	Yes	Medication did not work	Unhappy with sprays
No	No	No	No	Yes	Requested crossover	Unhappy with sprays
No	No	Yes	No	No	NA	
No	No	No	Yes	No	NA	
No	No	Yes	Yes	No	NA	
No	No	Yes	Yes	No	NA	
No	Yes	Yes	No	Yes	Had a nosebleed when using the spray	Side effects
No	No	No	No	Yes	Patient stated no improvement; requested surgery	Unhappy with sprays
No	No	No	No	Yes	Would like septoplasty. Will continue using nasal sprays until surgery	Unhappy with sprays
No	No	Yes	No	No	NA	
No	No	Yes	No	No	NA	
No	No	No	No	Yes	Sprays not as effective as participant would like	Unhappy with sprays
No	No	Yes	Yes	No	NA	
No	No	No	No	Yes	Patient stated not much improvement	Unhappy with sprays
No	No	No	Yes	No	NA	
		Yes			NA	
No	No	No	No	Yes	Did not find sprays beneficial	Unhappy with sprays
No	No	Yes	No	No	NA	
				Yes	Symptoms not improving	Unhappy with sprays

TABLE 32 Reasons for discontinuation of treatment for participants randomised to medical management (*n* = 71) (*continued*)

Concerns about time	Side effects of spray	Unhappy with spray	Worse symptoms	Other reason	Other reason text	Recategorisation of 'other'
No	No	Yes	Yes	No	NA	
No	No	Yes	No	No	NA	
No	No	Yes	No	No	NA	
No	No	Yes	No	No	NA	
No	No	No	No	Yes	Had septoplasty before 6 months was completed of the medication. This was a local administration error	
	Yes	Yes		Yes	Wanted to have surgery following epistaxis	
No	No	Yes	No	No	NA	
No	No	No	No	Yes	Felt little improvement	Unhappy with sprays
No	No	No	No	Yes	Patient requested surgery	Unhappy with sprays
No	No	Yes	No	No	NA	
No	No	No	Yes	No	NA	
				Yes	Did not make a difference	Unhappy with sprays
No	No	No	No	Yes	Patient feels their breathing is not improving	Unhappy with sprays
No	No	No	No	Yes	Patient requested septoplasty	Unhappy with sprays
No	No	Yes	No	No	NA	
No	No	No	No	Yes	Not getting sufficient benefit from the sprays	Unhappy with sprays
No	No	No	No	Yes	Job position changed so was unable to continue with the trial	
No	No	Yes	No	No	NA	
No	No	Yes	Yes	No	NA	
				Yes	Changed mind to a preference for surgery	Unhappy with sprays
No	No	Yes	No	Yes	To have septoplasty	Unhappy with sprays
No	No	Yes	No	No	NA	
No	No	Yes	No	No	NA	
No	No	No	No	Yes	Requested surgery; still has high NOSE score	Unhappy with sprays
No	No	Yes	No	No	NA	
No	Yes	No	No	No	NA	
No	No	No	No	Yes	To have septoplasty	Unhappy with sprays
				Yes	Would like septoplasty	Unhappy with sprays
No	No	No	No	Yes	Ineffective	Unhappy with sprays
No	No	No	No	Yes	Symptoms no better with the spray	Unhappy with sprays
No	No	No	No	Yes	Did not think it helped	Unhappy with sprays

continued

TABLE 32 Reasons for discontinuation of treatment for participants randomised to medical management (*n* = 71) (*continued*)

Concerns about time	Side effects of spray	Unhappy with spray	Worse symptoms	Other reason	Other reason text	Recategorisation of 'other'
No	Yes	No	No	No	NA	
No	No	Yes	No	No	NA	
No	No	Yes	Yes	Yes	Symptoms decreased but not sleeping well: spray not working	Unhappy with sprays
No	No	Yes	No	No	NA	
No	Yes	Yes	Yes	No	NA	
Yes	Yes	No	No	Yes	Symptoms have remained the same	Unhappy with sprays
No	No	No	Yes	No	NA	
No	No	Yes	No	No	NA	

NA, not applicable.

TABLE 33 Summary of medical history (baseline)

Medical history	Trial arm, *n* (%)		Overall (*N* = 378), *n* (%)	Non-randomised (*N* = 45), *n* (%) or *n*
	Septoplasty (*N* = 188)	Medical management (*N* = 190)		
Is overall sense of blocked nose bilateral or unilateral?				
Bilateral	79 (42)	77 (41)	156 (41)	11 (24)
Unilateral	109 (58)	113 (59)	222 (59)	7 (16)
Which side is worst?				
Left side worse	87 (46)	84 (44)	171 (45)	5
Right side worse	80 (43)	82 (43)	162 (43)	7
Both sides equal	21 (11)	24 (13)	45 (12)	6
Does blockage change from side to side and/or is it cyclical?				
Yes	52 (72)	49 (26)	101 (27)	1
No	136 (28)	140 (74)	No	136 (28)
Missing	0 (0)	1 (< 1)	1 (< 1)	0
Is there history of nasal trauma?				
Yes	79 (42)	95 (50)	174 (46)	8
No	109 (58)	95 (50)	204 (54)	10
If so, what was approximate age of patient (in years)				
n (% of history of nasal trauma)	78 (99)	95 (100)	173 (99)	8 (100)
Median (IQR)	21 (15–37)	17 (14–26)	19 (15–31)	15 (10.5–17)
Mean (SD)	28.0 (17.3)	20.7 (13.0)	24.0 (15.5)	15.6 (9.8)
Range (minimum, maximum)	(5, 78)	(1, 61)	(1, 78)	(3, 37)

TABLE 33 Summary of medical history (baseline) (*continued*)

Medical history	Trial arm, *n* (%)		Overall (*N* = 378), *n* (%)	Non-randomised (*N* = 45), *n* (%) or *n*
	Septoplasty (*N* = 188)	Medical management (*N* = 190)		
Did this nasal trauma result in definite change in nasal obstruction?				
Yes	48 (61)	62 (65)	110 (63)	7
No	30 (38)	32 (34)	62 (36)	1
missing	1 (1)	1 (1)	2 (1)	
Smoking status				
Current smoker	24 (13)	37 (19)	61 (16)	2
Ex-smoker	54 (29)	54 (28)	108 (29)	1
Never smoked	110 (59)	99 (52)	209 (55)	16

TABLE 34 Summary of clinical examination

Clinical exam	Trial arm, *n* (%)		Overall (*N* = 378), *n* (%)	Non-randomised (*N* = 45), *n*
	Septoplasty (*N* = 188)	Medical management (*N* = 190)		
If the patient is having surgery, would it be appropriate to reduce the inferior turbinate?				
Yes	132 (70)	150 (79)	282 (75)	7
No	52 (28)	32 (17)	84 (22)	2
Not applicable	4 (2)	8 (4)	12 (3)	6
To which side does the nasal septum deflect, so diminishing the airway?				
Right	79 (42)	67 (35)	146 (39)	9
Left	71 (38)	86 (45)	157 (42)	5
Both	38 (20)	37 (19)	75 (20)	1
Neither	0 (0)	0 (0)	0 (0)	0
Please specify the area of septum deflecting into that airway (right airway)				
(Right + both) septoplasty, *n* = 117; medical management, *n* = 104; total, *N* = 221	116 (99)	104 (100)	220 (> 99)	
Anterior	46 (39)	53 (51)	99 (45)	
Posterior	13 (11)	15 (14)	28 (13)	
Upper	11 (9)	8 (8)	19 (9)	
Lower	13 (11)	11 (11)	24 (11)	
All	30 (26)	16 (15)	46 (21)	
None	3 (3)	1 (< 1)	4 (2)	5
Missing	1 (< 1)	0 (0)	1 (< 1)	

continued

TABLE 34 Summary of clinical examination (*continued*)

Clinical exam	Trial arm, *n* (%)		Overall (*N* = 378), *n* (%)	Non-randomised (*N* = 45), *n*
	Septoplasty (*N* = 188)	Medical management (*N* = 190)		
Please specify the area of septum deflecting into that airway (left airway)				
(Left + both) septoplasty, *n* = 109; medical management, *n* = 123; total, *N* = 232	108 (99)	123 (100)	231 (> 99)	
Anterior	43 (39)	50 (41)	93 (40)	3
Posterior	17 (16)	19 (15)	36 (16)	0
Upper	8 (7)	8 (7)	16 (7)	0
Lower	12 (11)	15 (12)	27 (12)	1
All	26 (24)	29 (24)	55 (24)	1
None	2 (2)	2 (2)	4 (2)	
Missing	1 (< 1)	0 (0)	1 (< 1)	

TABLE 35 Summary of endoscopy findings

Endoscopy findings	Trial arm, *n* (%)		Overall (*N* = 378), *n* (%)	Non-randomised (*N* = 45), *n*
	Septoplasty (*N* = 188)	Medical management (*N* = 190)		
Right inferior turbinate enlarged?				
Yes	89 (47)	110 (42)	199 (53)	8
No	99 (53)	80 (58)	179 (47)	7
Left inferior turbinate enlarged?				
Yes	97 (52)	94 (49)	191 (51)	10
No	91 (48)	95 (50)	186 (49)	5
Missing	0 (0)	1 (< 1)	1 (< 1)	
Observer-rated airway block				
≤50%	53 (28)	52 (27)	105 (28)	2
> 50%	135 (72)	138 (73)	273 (72)	13
Evidence of adhesions?				
Yes	2 (1)	2 (1)	4 (1)	0
No	186 (99)	188 (99)	374 (99)	15
Side of adhesions?				
Left	0 (0)	0 (0)	0 (0)	
Right	0 (0)	2 (100)	2 (50)	
Both	1 (50)	0 (0)	1 (25)	
Not applicable	1 (50)	0 (0)	1 (25)	
Evidence of perforation?				
Yes	1 (< 1)	0 (0)	1 (< 1)	0
No	187 (> 99)	190 (100)	377 (> 99)	15

TABLE 36 Time in minutes of rhinospirometer measurement following decongestant

Timing of decongestant measurement times	Septoplasty arm (*n* = 188)	Medical management arm (*n* = 190)	Overall (*n* = 378)
Start time: baseline			
n (%)	188	190	378
Time			
Median (IQR)	10 (7–12)	10 (7–14)	10 (7–13)
Mean (SD)	10.3 (4.2)	11.4 (5.6)	10.9 (5.0)
Range (minimum, maximum)	(5, 27)	(5, 33)	(5, 33)
End time: baseline			
n (%)	188	189	377
Time			
Median (IQR)	15 (12.5–18)	15 (12–20)	15 (12–20)
Mean (SD)	16.1 (5.4)	17.2 (7.2)	16.6 (6.4)
Range (minimum, maximum)	(8, 35)	(7, 50)	(7, 50)
Start time: 6 months			
n (%)	128	123	251
Time			
Median (IQR)	10 (7–13)	10 (6–14)	10 (7–13)
Mean (SD)	10.9 (5.6)	10.6 (5.4)	10.7 (5.5)
Range (minimum, maximum)	(5, 38)	(5, 35)	(5, 38)
End time: 6 months			
n (%)	127	124	251
Time			
Median (IQR)	15 (12–19)	14 (11–19)	14 (11–19)
Mean (SD)	15.5 (5.9)	15.5 (6.1)	15.5 (6.0)
Range (minimum, maximum)	(7, 43)	(3, 36)	(3, 43)
Start time: 12 months			
n (%)	71	73	144
Time			
Median (IQR)	10 (7–16)	10 (7–15)	10 (7–16)
Mean (SD)	12.0 (6.2)	12.2 (6.8)	12.1 (6.5)
Range (minimum, maximum)	(5, 33)	(5, 46)	(5, 46)
End time: 12 months			
n (%)	70	73	143
Time			
Median (IQR)	14 (12–20)	15 (11–21)	15 (11–21)
Mean (SD)	16.9 (8.0)	16.8 (7.8)	16.8 (7.8)
Range (minimum, maximum)	(8, 54)	(8, 57)	(8, 57)

TABLE 37 Data completeness at baseline (visit 1), at the 6-month follow-up (visit 2) and at the 12-month follow-up (visit 3)

		Septoplasty arm (*N* = 188), *n* (%)			Medical management arm (*N* = 190), *n* (%)		
	CRF	Missing	Partial	Complete	Missing	Partial	Complete
Baseline visit 1*	Baseline demographics	0 (0)	2 (1)	186 (99)	0 (0)	0 (0)	190 (100)
	Clinical examination nasal endoscopy						
	1. The side of the convexity	0 (0)	0 (0)	188 (100)	0 (0)	0 (0)	190 (100)
	2. The side of deflection	0 (0)	0 (0)	188 (100)	0 (0)	0 (0)	190 (100)
	3. Endoscopy findings	0 (0)	0 (0)	188 (100)	0 (0)	0 (0)	190 (100)
	4. Extent of the airway block by the septum	0 (0)	0 (0)	188 (100)	0 (0)	0 (0)	190 (100)
	SNOT-22	0 (0)	2 (1)	186 (99)	0 (0)	2 (1)	188 (99)
	NOSE	0 (0)	0 (0)	188 (100)	0 (0)	0 (0)	190 (100)
	DOASS (post decongestion)	1 (< 1)	N/A	187 (99)	2 (1)	N/A	188 (99)
	Measurements of nasal patency[a]						
	1. PNIF (forced sniff) (maximum of three repeats)	0 (0)	0 (0)	188 (100)	0 (0)	0 (0)	190 (100)
	2. NPR (MIV) (mean of three repeats)	0 (0)	0 (0)	188 (100)	1 (< 1)	2 (1)	187 (98)
	3. NPR (tidal breathing)	1 (< 1)	0 (0)	187 (> 99)	1 (< 1)	2 (1)	187 (98)
Surgery	Post-surgery CRF [for those receiving surgery as randomised (*n* = 166)]	42 (25)	0 (0)	124 (75)	N/A	N/A	N/A
	Safety follow-up telephone call 2 weeks post surgery (*n* = 166)	42 (25)	N/A	124 (75)	N/A	N/A	N/A
Medical management	Safety follow-up telephone call 2 weeks post randomisation in the medical management arm (*n* = 190)	N/A	N/A	N/A	39 (21)	N/A	151 (79)
6-month follow-up visit	SNOT-22 (MACRO or Castor)	36 (19)	2 (1)	150 (80)	35 (18)	3 (2)	152 (80)
	NOSE	43 (23)	1 (< 1)	144 (77)	45 (24)	0 (0)	145 (76)
	DOASS (post decongestion)	59 (31)	N/A	129 (69)	64 (34)	N/A	126 (66)
	Clinical examination nasal endoscopy*						
	1. PNIF (forced sniff) (maximum of three repeats)	61 (32)	0 (0)	127 (68)	66 (35)	0 (0)	123 (65)
	2. NPR (MIV) (mean of three repeats)	61 (32)	2 (1)	125 (66)	66 (35)	0 (0)	124 (65)
	3. NPR (tidal breathing)	61 (32)	1 (< 1)	126 (67)	66 (35)	2 (1)	122 (64)
12-month follow-up visit	SNOT-22 (MACRO or Castor)	63 (34)	1 (< 1)	124 (66)	62 (33)	3 (2)	125 (66)
	NOSE	78 (41)	0 (0)	110 (59)	69 (36)	0 (0)	121 (64)
	DOASS (post decongestion)	115 (61)	N/A	73 (39)	109 (57)	N/A	81 (43)
	Clinical examination nasal endoscopy*						
	1. PNIF (forced sniff) (maximum of three repeats)	118 (63)	0 (0)	70 (37)	116 (61)	1 (< 1)	73 (38)
	2. NPR (MIV) (mean of three repeats)	117 (62)	1 (< 1)	70 (37)	116 (61)	1 (< 1)	73 (38)
	3. NPR (tidal breathing)	117 (62)	1 (< 1)	70 (37)	116 (61)	2 (1)	72 (38)

Castor, data collection tool; CRF, case report form; MACRO, database; N/A, not applicable.
a Measurements of nasal patency were originally planned to be taken at all visits, but could not be measured at some follow-up visits during national COVID-19 pandemic restrictions (March 2020 onwards).

TABLE 38 Compliance for SNOT-22 completion at follow-up visits by randomised arm

Trial arm	6 months (primary end point)			12 months		
	Number completed	Complied,[a] *n* (%)	Not complied,[b] *n* (%)	Number completed	Complied,[c] *n* (%)	Not complied,[d] *n* (%)
Septoplasty	152	126 (83)	26 (17)	125	81 (65)	44 (35)
Medical management	155	128 (83)	27 (17)	126	84 (67)	42 (33)

a Complied within the window specified in protocol and SAP (±2 weeks) around the expected visit date (at 12 months from randomisation).
b Early (before 6 months −2 weeks) or late (after 6 months + 4 weeks).
c Complied 12 months −2 weeks to + 2 weeks.
d Early (before 12 months −2 weeks) or late (after 12 months + 2 weeks).

TABLE 39 Summary of septoplasty operative steps

Steps of septoplasty	Septoplasty (*N* = 166), *n* (%)	Medical management (*N* = 51), *n*
Closed approach	155 (93)	13
Unilateral hemitransfixion incision	134 (81)	13
Unilateral mucoperichondrial flap	63 (38)	6
Bilateral mucoperichondrial flap	103 (62)	8
Cartilage resection	146 (88)	12
Cartilage scoring	10 (6)	3
Septal cartilage grafting	0 (0)	0
Maxillary crest medialised	90 (54)	4
Mattress sutures to close	133 (80)	12
Sutures to hemitransfixion incision	141 (85)	13
Nasal splints	36 (22)	2
Nasal packing	45 (27)	3
Unilateral turbinate surgery	92 (55)	7
Turbinate reduced	91 (55)	8
Turbinate resected	11 (7)	0

TABLE 40 Data completion: septoplasty (septoplasty arm only, *n* = 166)

Septoplasty step	Frequency (% of 166)
Was septoplasty ± turbinate reduction carried out?	
No	4 (2)
Yes	156 (94)
Missing	6 (4)
Did the patient stay overnight in hospital?	
No	146 (88)
Yes	14 (8)
Missing	6 (4)
If yes (stayed overnight), how many nights?	All 14 stayed 1 night
Grade of most senior operative	
Surgeon	128 (77)
Consultant	17 (10)
Associate specialist	16 (10)
Other	5 (3)
Grade of most senior anaesthetist	
Consultant	144 (87)
Associate specialist	7 (4)
Staff grade	3 (2)
Other	7 (4)
Missing	5 (3)
Closed approach	
No	2 (1)
Yes	155 (93)
Missing	9 (5)
Unilateral hemitransfixion incision	
No	25 (15)
Yes	134 (81)
Missing	7 (4)
Unilateral mucoperichondrial flap	
No	95 (57)
Yes	63 (38)
Missing	8 (5)
Bilateral mucoperichondrial flap	
No	55 (33)
Yes	103 (62)
Missing	8 (5)

TABLE 40 Data completion: septoplasty (septoplasty arm only, *n* = 166) (*continued*)

Septoplasty step	Frequency (% of 166)
Cartilage resection	
No	12 (7)
Yes	146 (88)
Missing	8 (5)
Cartilage scoring	
No	146 (88)
Yes	10 (6)
Missing	10 (6)
Maxillary crest medialised	
No	64 (39)
Yes	90 (54)
Missing	12 (7)
Mattress sutures to close	
No	24 (14)
Yes	133 (80)
Missing	9 (5)
Sutures to hemitransfixion incision	
No	15 (9)
Yes	141 (85)
Missing	10 (6)
Nasal splints	
No	123 (74)
Yes	36 (22)
Missing	7 (4)
Nasal packing	
No	114 (69)
Yes	45 (27)
Missing	7 (4)
Unilateral inferior turbinate surgery	
No	63 (38)
Yes	92 (55)
Missing	11 (7)
Unilateral?	
No	53 (32)
Yes	78 (47)
Missing	35 (21)

continued

TABLE 40 Data completion: septoplasty (septoplasty arm only, *n* = 166) (*continued*)

Septoplasty step	Frequency (% of 166)
Inferior turbinate reduced	
No	63 (38)
Yes	91 (55)
Missing	12 (7)
Inferior turbinate resected	
No	143 (86)
Yes	11 (7)
Missing	12 (7)

TABLE 41 Duration of septoplasty (minutes)

	Septoplasty participants (*N* = 166)
n (% of all surgeries)	159 (96)
Duration (minutes)	
Median (IQR)	56 (44–65)
Mean (SD)	56.2 (17.9)
Range (minimum, maximum)	(17, 105)
Missing, *n* (%)	7 (4)

TABLE 42 Nasal spray use at the 6-month visit (medical management arm, *N* = 190)

Question and answers	6 months only
Over the previous month, have you used the NAIROS medication (nasal steroid and/or saline sprays)?, *n* (%)	122 (64)
• Not at all or rarely, *n*	17
• More than one-quarter of the days, *n*	1
• More than half of the days, *n*	3
• More than three-quarters of the days, *n*	14
• Almost always (> 90% of the days), *n*	87
On the days you used the sprays, has it usually been	
• Once	65
• Twice	48

TABLE 43 Number who used saline/steroid spray and returned information on how much used (medical management arm, *N* = 190)

Question and answer	Saline spray (*N* = 69)	Steroid spray (*N* = 65)
Saline/steroid bottles used: median (IQR) for *n* who returned this information	3.5 (2.5–5)	4 (3–5.5)
Are you still using the spray?, *n* (%)	132 (69)	132 (69)
Responded 'yes', *n*	90	96
Responded 'no', *n*	42	36
If no, about how long ago did you stop using it?, *n*	42	36
Within the previous month, *n*	25	23
2–3 months ago, *n*	13	8
> 3 months ago, *n*	4	4
Did not use it at all, *n*	0	1
Why did you stop using it?		
Do not think it helped	18	19
Think it gave me side effects[a]	6	5
Other reason[a]	19	14

a other reasons and side effects are summarised in *Table 44*.

TABLE 44 Line listing of 'other' and 'side effects' given for stopping using nasal sprays

Reasons for stopping using sprays (reason or side effect)	Saline spray, *n* (%)	Steroid spray, *n* (%)
End of 6 months/ran out/finished supplies (other reason)	15 (60)	9 (53)
Nasal pain and/or bleeding (side effect)	3 (12)	3 (18)
Not helpful (other reason)	2 (8)	0 (0)
Symptoms eased	0 (0)	1 (6)
Reflux/gag (side effect)	1 (4)	0 (0)
Rhinorrhoea (side effect)	1 (4)	1 (6)
Laziness (other reason)	1 (4)	0 (0)
In prison (other reason)	1 (4)	1 (6)
SAE after accident; had surgery	0 (0)	1 (6)
Occupational reasons	0 (0)	1 (6)
No reason given (side effect)	1 (4)	0 (0)
Total	25 (100)	17[a] (100)

a Total for steroids of side effects and 'other' reasons is 17 as two participants chose both options.

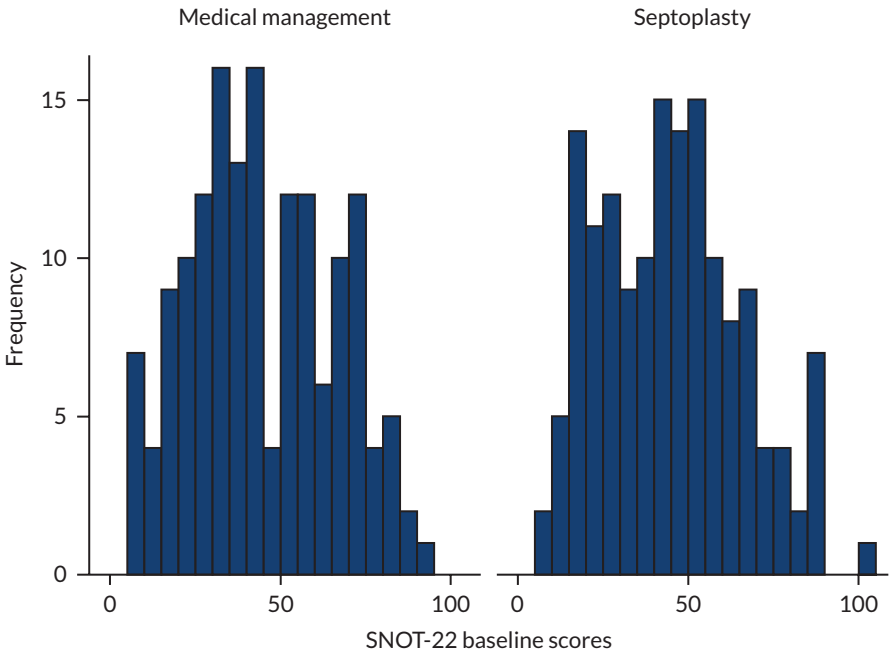

FIGURE 23 Baseline SNOT-22 scores, by randomised arm.

TABLE 45 The SNOT-22 scores at 12 months

SNOT-22 scores at 12 months, ITT population	Trial arm		Overall (ITT, *N* = 307)
	Septoplasty (ITT, *N* = 152)	Medical management (ITT, *N* = 155)	
ITT population, *n* (% of ITT *n*)	119 (65)	125 (81)	244 (79)
Median (IQR)	15 (8–30)	29 (12–45)	20.5 (10–39)
Mean (SD)	21.2 (19.0)	30.4 (21.6)	25.9 (20.9)
95% CI about mean	17.7 to 24.6	26.6 to 34.3	23.3 to 28.5
Minimum, maximum	0, 91	0, 78	0, 91

TABLE 46 Timing of septoplasty in relation to the primary end point for those randomised to medical management who received non-trial septoplasty (*n* = 51)

Medical management non-trial surgery	Frequency (all surgeries)	ITT (with baseline and 6-month SNOT-22 score)
Surgery before primary end point (6-month SNOT-22 score)	9	5
Surgery between 6 and 12 months	37	37
Surgery beyond 12 months (12-month SNOT-22 score)	4	4
Surgery date unknown	1	0
Total	51	46

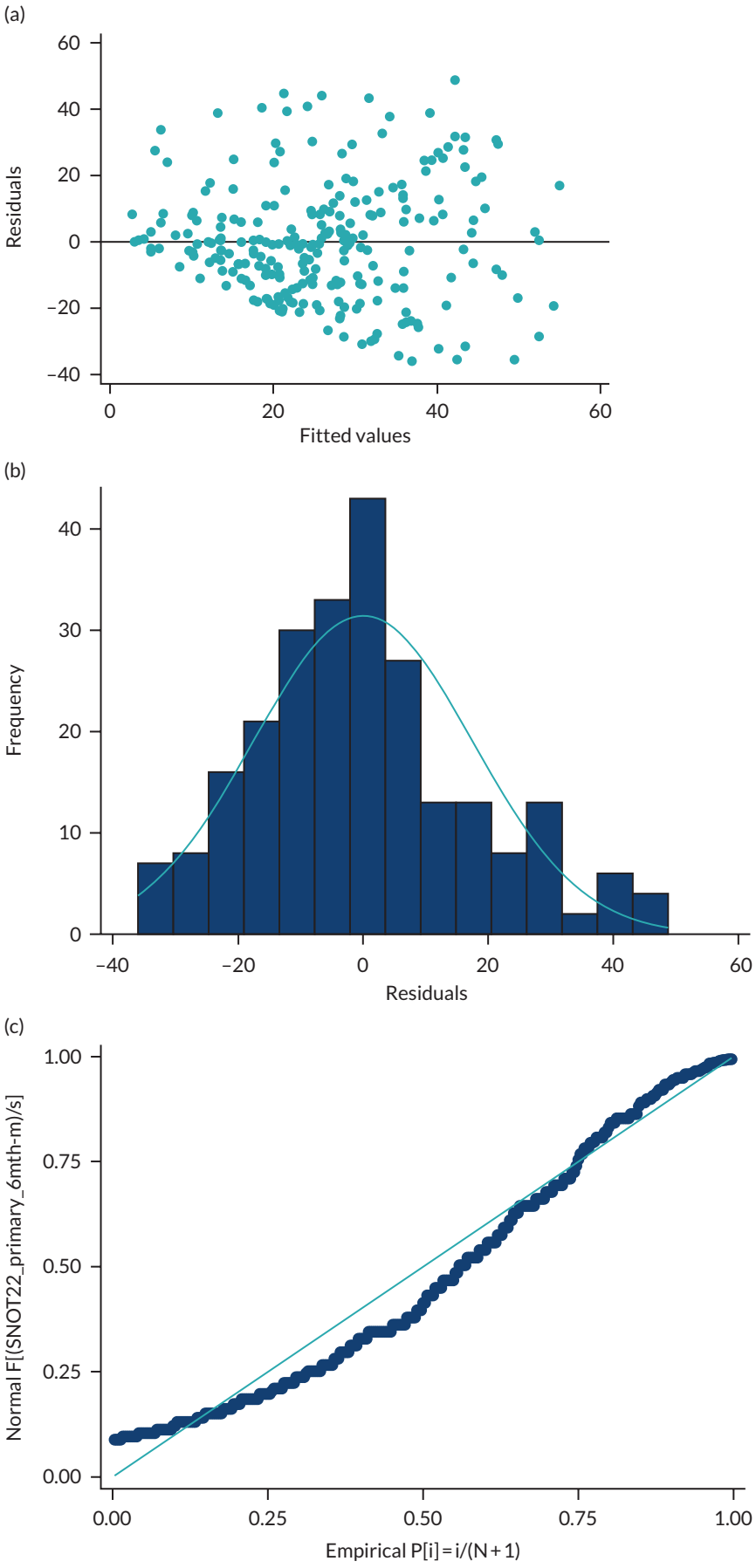

FIGURE 24 Residual analysis. (a) Residuals vs. fitted values; (b) histogram of residuals; (c) normal probability plot of the residuals; and (d) standardised residuals vs. fitted values. (*continued*)

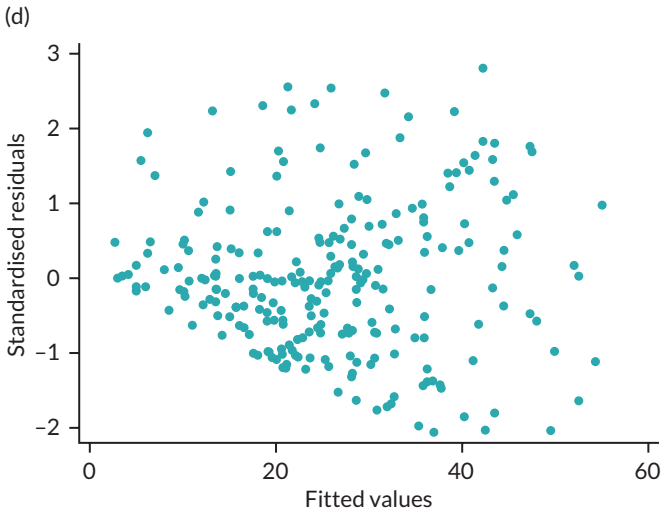

FIGURE 24 Residual analysis. (a) Residuals vs. fitted values; (b) histogram of residuals; (c) normal probability plot of the residuals; and (d) standardised residuals vs. fitted values.

TABLE 47 Univariable assessment of baseline demographic, selected medical and endoscopy variables (including transformed continuous covariates) against the primary outcome (ITT population)

Covariate	Number	Coefficient	SE	Test statistic	*p*-value
Age (continuous)	307	0.085	0.087	0.98	0.328
Age log transform	307	2.674	3.356	0.80	0.426
Age complex transform (age3)	307	0.000	0.000	1.27	0.204
Ethnicity (reference: white)	272				
Asian	20	0.739	5.154	0.14	0.886
Other Asian	3	−5.477	12.915	−0.42	0.672
Other ethnic origin	10	1.695	7.163	0.24	0.813
Missing	2	N/A	N/A	N/A	N/A
Site (reference: site 1 – Newcastle)	62				
2. Great Yarmouth	19				0.093
3. Bradford	12				0.164
4. Wigan	12				0.595
5. Darlington	7				0.459
6. Plymouth	12				0.948
7. Dundee	17				0.018
8. Aberdeen	34				0.294
9. Stockport	13				0.272
10. London	12				0.805
11. Newport	11				0.070
12. Birmingham	12				0.577
13. Carlisle	10				0.494
14. Aintree	17				0.072
15. Leeds	25				0.573
16. Lanarkshire	17				0.585
17. Salisbury	15				0.452

TABLE 47 Univariable assessment of baseline demographic, selected medical and endoscopy variables (including transformed continuous covariates) against the primary outcome (ITT population) (*continued*)

Covariate	Number	Coefficient	SE	Test statistic	*p*-value
Smoking history (reference: smoker)	46				
Ex-smoker	88	−4.728	3.953	−1.20	0.233
Never smoked	173	−11.434	3.605	−3.17	0.002
Block (reference: bilateral)	128				
Unilateral	179	−1.506	2.561	−0.59	0.557
Nasal trauma (reference: yes)	140				
No	167	−2.316	2.533	−0.91	0.361
Reduce turbinate (reference: yes)	230				
No	66	−5.410	3.081	−1.76	0.080
Not applicable	11				
Airway block observer-rated scale (reference: ≤50%)	85				
> 50%	222	−1.855	2.822	−0.66	0.511
Baseline absolute subjective DOASS	304	2.022	2.901	0.70	0.486
Complex transform (baseline absolute subjective DOASS$^{-0.5}$)	304	0.788	1.449	0.54	0.587
Log baseline absolute subjective DOASS	286	−0.238	1.803	−0.13	0.895
Baseline worst DOASS	304	−1.257	0.617	−2.04	0.043
Complex transform (baseline worst DOASS$^{-0.5}$)	304	15.108	6.296	2.40	0.017
Log baseline worst DOASS	304	−4.689	2.003	−2.34	0.020
Baseline PNIF (post decongestant)	307	−0.048	0.025	−1.94	0.054
Log baseline PNIF (post decongestant)	305	−0.312	1.694	−0.18	0.854
Complex transform (best is linear^{-1})	N/A	N/A	N/A	N/A	N/A
Baseline absolute NPR (post decongestant)	307	3.465	4.114	0.84	0.400
Log baseline absolute NPR (post decongestant)	305	−0.122	1.079	−0.01	0.991
Complex transform ($^{-1}$)	307	0.034	0.027	1.22	0.224
Baseline absolute tidal breathing ratio (post decongestant)	306	0.552	4.082	0.14	0.893
Log baseline absolute tidal breathing (post decongestant)	305	0.485	1.164	0.42	0.677
Complex transform (^{0})	306	0.686	1.170	0.59	0.558
Medical physics-derived endoscopy variables					
Absolute NPR	273	−0.889	4.182	−0.21	0.832
Log absolute NPR	273	0.204	1.220	0.17	0.867
Complex transform (^{3})	273	−4.391	4.316	−1.02	0.310
Absolute decongestant NPR	270	−4.021	5.684	−0.71	0.480
Log absolute decongestant NPR	165	−0.535	1.143	−0.47	0.640
Complex transform ($^{-2}$)	270	8.34×10^{-6}	7.60×10^{-6}	1.10	0.274

continued

TABLE 47 Univariable assessment of baseline demographic, selected medical and endoscopy variables (including transformed continuous covariates) against the primary outcome (ITT population) (*continued*)

Covariate	Number	Coefficient	SE	Test statistic	*p*-value
Total maximum flow rate	273	−0.005	0.005	−1.06	0.292
Log total maximum flow rate	273	−3.407	2.699	−1.26	0.208
Complex transform ($^{-2}$)	273	280129.6	118248.3	2.37	0.019
Median tidal volume	264	−0.003	0.003	−1.17	0.245
Log median tidal volume	264	−5.123	1.979	−2.58	0.011
Complex transform ($^{-1}$)	264	1995.859	627.311	3.18	0.002

SE, standard error.

TABLE 48 Model 3 after forward selection applied

Primary outcome measure: SNOT-22 score at 6 months	Coefficient	SE of coefficient	Test statistic	*p*-value	95% CI of coefficient
Arm: (reference category: medical management)					
Septoplasty	−20.426	1.918	−10.65	< 0.001	−24.203 to −16.650
Baseline SNOT-22 score	0.454	0.063	7.16	< 0.001	0.329 to 0.578
Gender (ref category: female)					
Male	1.158	2.075	0.56	0.577	−2.929 to 5.245
NOSE severity (continuous)	0.134	0.075	1.78	0.076	−0.014 to 0.283
Reciprocal of median tidal volume	1446.909	475.713	3.04	0.003	510.134 to 2383.685
Constant	6.198	4.630	1.34	0.182	−2.919 to 15.315

SE, standard error.

Notes
n = 264, adjusted R^2 = 0.4859; probability ≥ F ≤ 0.0001.

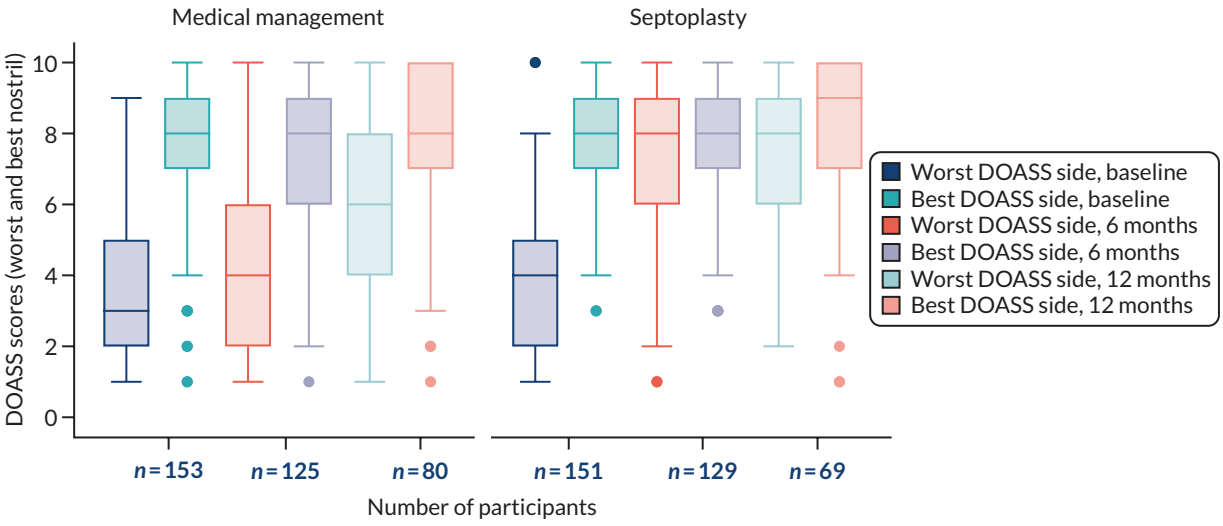

FIGURE 25 The DOASS raw data (ITT population). Graphs by arm. ITT population: medical management, n = 155; septoplasty, n = 152.

TABLE 49 The DOASS worst- and better-side measurements (worst = lower score)

DOASS measurements, ITT population	Worst side			Better side		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
Baseline						
ITT population, *n* (% of *N*)	151 (80)	153 (81)	304 (80)	151 (80)	153 (81)	304 (80)
Median (IQR)	4 (2–5)	3 (2–5)	4 (2–5)	8 (7–9)	8 (7–9)	8 (7–9)
Mean (SD)	3.9 (2.0)	3.7 (2.1)	3.8 (2.0)	7.7 (1.8)	7.7 (1.9)	7.7 (1.8)
95% CI about mean	3.6 to 4.2	3.3 to 4.0	3.6 to 4.0	7.4 to 8.0	7.4 to 8.0	7.5 to 7.9
Minimum, maximum	1, 10	1, 9	1, 10	3, 10	1, 10	1, 10
6 months (primary end point)						
ITT population, *n* (% of *N*)	129 (69)	125 (66)	254 (67)	129 (69)	125 (66)	254 (67)
Median (IQR)	8 (6–9)	4 (2–6)	6 (4–8)	8 (7–9)	8 (6–9)	8 (7–9)
Mean (SD)	7.2 (2.4)	4.6 (2.4)	5.9 (2.7)	8.1 (1.8)	7.4 (2.2)	7.8 (2.0)
95% CI about mean	7.8 to 8.4	7.1 to 7.8	5.6 to 6.2	7.8 to 8.4	7.1 to 7.8	7.5 to 8.0
Minimum, maximum	1, 10	1, 10	1, 10	3, 10	1, 10	1, 10
12 months						
ITT population, *n* (% of *N*)	69 (37)	80 (42)	149 (39)	69 (37)	80 (42)	149 (39)
Median (IQR)	8 (6–9)	6 (4–8)	7 (5–9)	9 (7–10)	8 (7–10)	9 (7–10)
Mean (SD)	7.3 (2.3)	6.0 (2.8)	6.6 (2.6)	8.1 (2.2)	8.0 (2.0)	8.0 (2.1)
95% CI about mean	6.8 to 7.9	5.4 to 6.7	6.2 to 7.1	7.6 to 8.6	7.5 to 8.4	7.7 to 8.4
Minimum, maximum	2, 10	1, 10	1, 10	1, 10	1, 10	1, 10

TABLE 50 Absolute subjective DOASS (ITT population)

Absolute subjective DOASS, ITT population	Baseline			6 months			12 months		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
ITT population, *n* (% of *N*)	151 (80)	153 (81)	304 (80)	129 (69)	125 (66)	254 (67)	69 (37)	80 (42)	149 (39)
Median (IQR)	0.3 (0.2–0.6)	0.3 (0.2–0.6)	0.3 (0.2–0.6)	0.1 (0.1–0.2)	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.1 (0.1–0.2)	0.2 (0.1–0.4)	0.1 (0.1–0.3)
Mean (SD)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.2 (0.2)	0.4 (0.2)	0.3 (0.2)	0.2 (0.2)	0.3 (0.2)	0.2 (0.2)
95% CI about mean	0.3 to 0.4	0.3 to 0.4	0.3 to 0.4	0.1 to 0.2	0.3 to 0.4	0.2 to 0.3	0.1 to 0.2	0.2 to 0.3	0.2 to 0.3
Minimum, maximum	0, 0.8	0, 0.8	0, 0.8	0, 0.8	0, 0.8	0, 0.8	0, 0.8	0, 0.8	0, 0.8

TABLE 51 Summary statistics for SNOT-22 subscales at baseline, 6 months and 12 months (ITT population)

	Septoplasty (*N* = 188)			Medical management (*N* = 190)			Overall (*N* = 378)		
SNOT-22 subscale	**Baseline**	**6 months**	**12 months**	**Baseline**	**6 months**	**12 months**	**Baseline**	**6 months**	**12 months**
Nasal (*n*)	152	152	119	155	155	125	307	307	244
Median (IQR)	16 (11.5–22)	6 (2–12)	6 (3–13)	15 (11–22)	14 (9–19)	10 (5–16)	16 (11–22)	10 (5–17)	8 (4–15)
Mean (SD)	17.0 (7.4)	7.8 (6.7)	8.2 (7.3)	16.3 (7.4)	14.5 (7.2)	11.3 (8.0)	16.6 (7.4)	11.2 (7.7)	9.8 (7.8)
95% CI	15.8 to 18.2	6.7 to 8.9	6.9 to 9.5	15.1 to 17.5	13.4 to 15.6	9.9 to 12.7	15.8 to 17.5	10.3 to 12.0	98.8 to 10.8
Minimum, maximum	3, 38	0, 38	0, 39	0, 33	0, 32	0, 31	0, 38	0, 38	0, 39
Sleep (*n*)	152	152	119	155	155	125	307	307	244
Median (IQR)	20 (10–29)	6 (0–13)	6 (1–16)	21 (12–29)	19 (8–29)	14 (4–22)	20 (11–29)	11 (3–23)	9 (2–20)
Mean (SD)	19.8 (11.1)	8.8 (9.8)	9.5 (10.0)	20.5 (11.0)	18.8 (11.7)	14.0 (11.0)	20.1 (11.0)	13.8 (11.9)	11.8 (10.7)
95% CI	18.0 to 21.6	7.2 to 10.4	7.7 to 11.3	18.7 to 22.2	16.9 to 20.6	12.0 to 16.0	18.9 to 21.4	12.5 to 15.2	10.5 to 13.2
Minimum, maximum	0, 40	0, 37	0, 35	0, 40	0, 40	0, 40	0, 40	0, 40	0, 40
Otological (*n*)	152	152	119	155	155	125	307	307	244
Median (IQR)	4 (2–7)	1 (0–3)	1 (0–2)	3 (1–7)	2 (0–6)	2 (0–5)	4 (1–7)	2 (0–5)	1 (0–4)
Mean (SD)	5.1 (4.5)	2.3 (3.2)	2.3 (3.7)	4.5 (4.3)	3.8 (4.1)	3.3 (3.9)	4.8 (4.4)	3.1 (3.7)	2.8 (3.8)
95% CI	4.3 to 5.8	1.8 to 2.8	1.6 to 2.9	3.8 to 5.2	3.2 to 4.5	2.6 to 4.0	4.3 to 5.3	2.6 to 3.5	2.3 to 3.3
Minimum, maximum	0, 20	0, 16	0, 17	0, 18	0, 19	0, 19	0, 20	0, 19	0, 19
Emotional (*n*)	152	152	119	155	155	125	307	307	244
Median (IQR)	1.5 (0–5)	0 (0–1)	0 (0–1)	2 (0–5)	2 (0–4)	1 (0–4)	2 (0–5)	0 (0–3)	0 (0–3)
Mean (SD)	2.7 (2.9)	1.0 (1.9)	1.2 (2.2)	2.8 (3.0)	2.4 (2.7)	1.8 (2.3)	2.7 (2.9)	1.7 (2.4)	1.5 (2.3)
95% CI	2.2 to 3.1	0.7 to 1.3	0.8 to 1.6	2.3 to 3.3	2.0 to 2.8	1.4 to 2.2	2.4 to 3.1	1.4 to 2.0	1.2 to 1.8
Minimum, maximum	0, 10	0, 9	0, 9	0, 10	0, 10	0, 9	0, 10	0, 10	0, 9

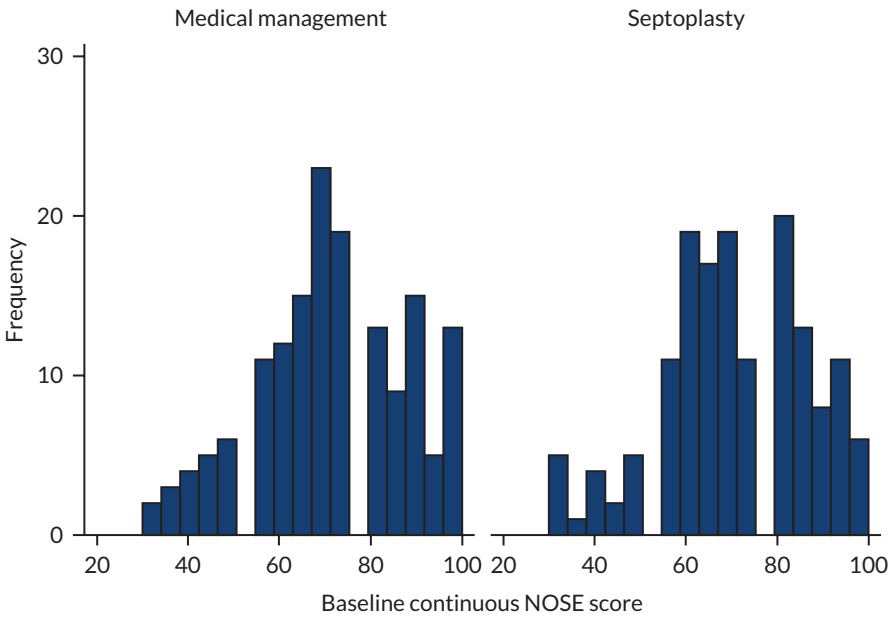

FIGURE 26 Distribution of baseline continuous NOSE scores, by allocated arm.

TABLE 52 Peak nasal inspiratory flow (l/minute, ITT population)

PNIF post-decongestant measurements, ITT population	Baseline			6 months			12 months		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
ITT population, *n* (% of *N*)	152 (81)	155 (82)	307 (81)	127 (68)	123 (65)	250 (66)	66 (35)	72 (38)	138 (37)
Median (IQR)	100 (60–130)	95 (69–138)	100 (65–130)	120 (80–160)	100 (70–140)	110 (75–150)	112.5 (80–150)	110 (70–160)	110 (80–160)
Mean (SD)	102.0 (51.2)	102.0 (49.4)	102.0 (50.2)	125.1 (61.7)	107.6 (48.4)	116.5 (56.2)	121.2 (62.1)	116.0 (50.7)	118.5 (56.3)
95% CI about mean	93.8 to 110.2	94.1 to 109.8	96.4 to 107.6	114.3 to 136.0	99.0 to 116.3	109.5 to 123.5	106.0 to 136.5	104.1 to 127.9	109.0 to 128.0
Minimum, maximum	0, 265	1, 270	0, 270	0, 320	1, 270	0, 320	1, 290	30, 230	1, 290

TABLE 53 Worse-side (lower) and better-side (higher) inhaled volumes from post-decongestant MIV rhinospirometry (using mean volumes from three measurements), ITT population

Time point	Worse side			Better side		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
Baseline						
ITT population, *n* (% of *N*)	152 (81)	155 (82)	307 (81)	152 (81)	155 (82)	307 (81)
Median (IQR)	0.5 (0.2–0.9)	0.4 (0.2–0.9)	0.5 (0.2–0.9)	1.4 (0.9–2.0)	1.4 (0.9–1.9)	1.4 (0.9–2.0)
Mean (SD)	0.6 (0.6)	0.6 (0.6)	0.6 (0.6)	1.5 (1.0)	1.5 (0.8)	1.5 (0.9)
95% CI about mean	0.5 to 0.7	0.5 to 0.7	0.5 to 0.7	1.4 to 1.7	1.3 to 1.6	1.4 to 1.6
Minimum, maximum	0, 5	0, 5	0, 5	0, 5	0, 5	0, 5
6 months (primary end point)						
ITT population, *n* (% of *N*)	126 (67)	123 (65)	249 (66)	126 (67)	123 (65)	249 (66)
Median (IQR)	1.0 (0.6–1.3)	0.7 (0.3–1.1)	0.8 (0.5–1.2)	1.4 (0.8–1.8)	1.4 (0.9–1.9)	1.4 (0.9–1.8)
Mean (SD)	1.0 (0.6)	0.7 (0.5)	0.9 (0.6)	1.4 (0.8)	1.4 (0.7)	1.4 (0.7)
95% CI about mean	0.9 to 1.1	0.6 to 0.8	0.8 to 0.9	1.3 to 1.6	1.3 to 1.6	1.3 to 1.5
Minimum, maximum	0, 2.7	0, 2.9	0, 2.9	0, 4.5	0, 3.5	0, 4.5
12 months						
ITT population, *n* (% of *N*)	66 (35)	72 (38)	138 (37)	66 (35)	72 (38)	138 (37)
Median (IQR)	1.1 (0.6–1.5)	0.9 (0.5–1.4)	1.0 (0.5–1.4)	1.3 (0.9–1.8)	1.4 (1.0–2.0)	1.3 (0.9–1.9)
Mean (SD)	1.1 (0.6)	0.9 (0.6)	1.0 (0.6)	1.3 (0.7)	1.5 (0.8)	1.4 (0.7)
95% CI about mean	1.0 to 1.3	0.8 to 1.1	0.9 to 1.1	1.2 to 1.5	1.3 to 1.7	1.3 to 1.6
Minimum, maximum	0.2, 3.0	0, 3.2	0, 3.2	0, 3.7	0.2, 3.8	0, 3.8

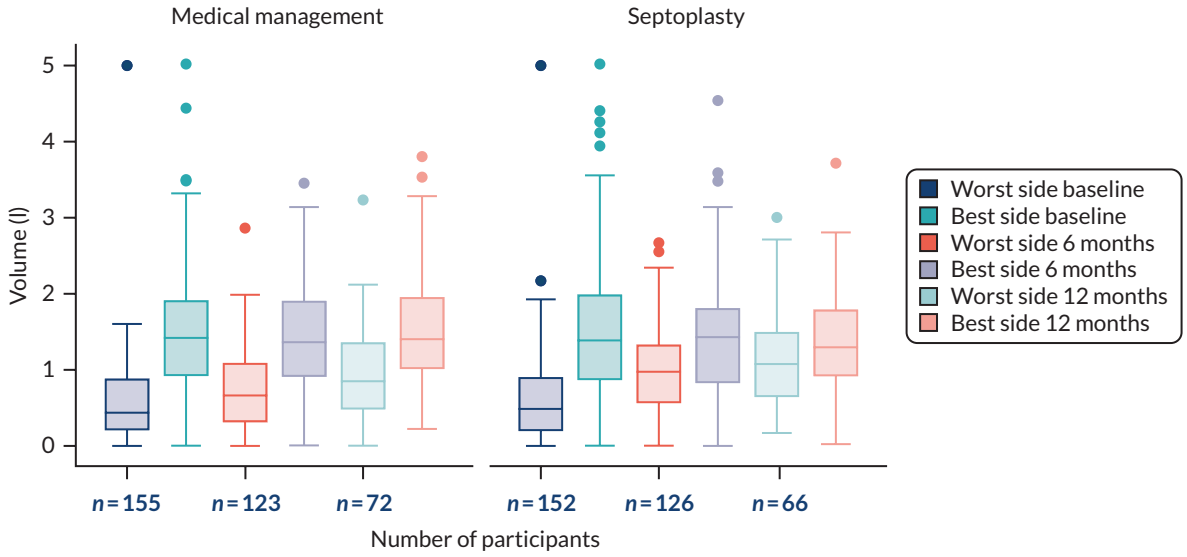

FIGURE 27 Worse-side (lower) and better-side (higher) inhaled volumes from post-decongestant MIV rhinospirometry (using mean volumes from three measurements), ITT population.

TABLE 54 Absolute MIV NPR post-decongestant measurements (using mean volumes from three measurements), ITT population

Absolute NPR post-decongestant measurements, ITT population	Baseline			6 months			12 months		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
ITT population, *n* (% of *N*)	152 (81)	155 (82)	307 (81)	126 (67)	123 (65)	249 (66)	66 (35)	72 (38)	138 (37)
Median (IQR)	0.3 (0.2–0.7)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.2 (0.1–0.4)	0.4 (0.1–0.6)	0.3 (0.1–0.5)	0.1 (0.1–0.3)	0.3 (0.1–0.5)	0.2 (0.1–0.4)
Mean (SD)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.3 (0.2)	0.4 (0.3)	0.3 (0.3)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)
95% CI about mean	0.4 to 0.5	0.4 to 0.5	0.4 to 0.5	0.2 to 0.3	0.4 to 0.5	0.3 to 0.4	0.2 to 0.3	0.3 to 0.4	0.2 to 0.3
Minimum, maximum	0, 1	0, 1	0, 1	0, 1	0, 1	0, 1	0, 0.9	0, 1	0, 1

TABLE 55 Worse-side (lower) and better-side (higher) inhaled volumes from post-decongestant, tidal breathing rhinospirometry (one measurement)

MIV (L)	Worst side			Better side		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
Baseline						
ITT population, *n* (% of *N*)	151 (80)	155 (82)	306 (81)	151 (80)	155 (82)	306 (81)
Median (IQR)	1.5 (0.6–2.5)	1.5 (0.7–2.4)	1.5 (0.6–2.5)	3.2 (3.0–3.4)	3.2 (3.0–3.4)	3.2 (3.0–3.4)
Mean (SD)	1.5 (1.0)	1.5 (1.0)	1.5 (1.0)	3.0 (0.8)	3.1 (0.7)	3.1 (0.7)
95% CI about mean	1.4 to 1.7	1.4 to 1.7	1.4 to 1.6	2.9 to 3.2	3.0 to 3.2	3.0 to 3.1
Minimum, maximum	0, 3.6	0, 3.3	0, 3.6	0.1, 5	0.4, 4.6	0.1, 5
6 months (primary end point)						
ITT population, *n* (% of *N*)	126 (67)	123 (65)	249 (66)	126 (67)	123 (65)	249 (66)
Median (IQR)	2.5 (1.5–3.1)	1.9 (1.0–3.0)	2.2 (1.2–3.1)	3.1 (2.6–3.3)	3.1 (2.8–3.3)	3.1 (2.7–3.3)
Mean (SD)	2.3 (1.0)	1.9 (1.1)	2.1 (1.1)	2.8 (0.9)	3.0 (0.7)	2.9 (0.8)
95% CI about mean	2.1 to 2.5	1.7 to 2.1	2.0 to 2.2	2.6 to 3.0	2.8 to 3.1	2.8 to 3.0
Minimum, maximum	0.1, 4.5	0, 4.6	0, 4.6	0.2, 5.0	0.6, 4.6	0.2, 5
12 months						
ITT population, *n* (% of *N*)	66 (35)	72 (38)	138 (37)	66 (35)	72 (38)	138 (37)
Median (IQR)	2.6 (2.0–3.2)	2.2 (1.1–3.1)	2.4 (1.4–3.1)	3.1 (2.5–3.4)	3.1 (2.7–3.3)	3.1 (2.6–3.3)
Mean (SD)	2.4 (1.0)	2.0 (1.1)	2.2 (1.1)	2.8 (0.9)	2.7 (1.0)	2.8 (0.9)
95% CI about mean	2.2 to 2.7	1.7 to 2.3	2.0 to 2.4	2.6 to 3.0	2.5 to 3.0	2.6 to 2.9
Minimum, maximum	0, 4.5	0, 3.7	0, 4.5	0.1, 3.8	0, 4.2	0, 4.2

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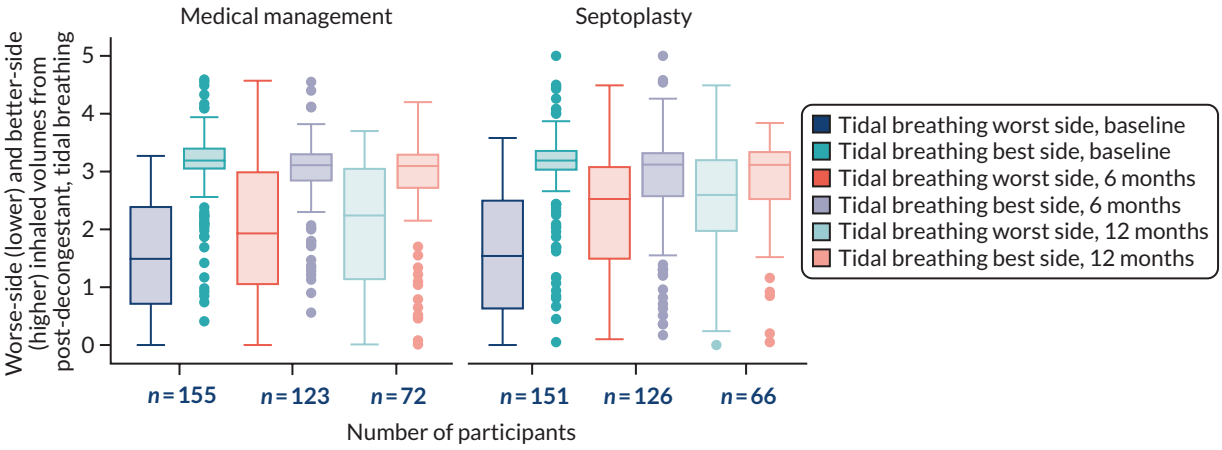

FIGURE 28 Worse-side (lower) and better-side (higher) inhaled volumes from post-decongestant, tidal breathing rhinospirometry, ITT population. Graphs by arm. ITT population: medical management, *n* = 155; septoplasty, *n* = 152.

TABLE 56 Summary statistics for absolute tidal breathing NPR

Absolute tidal breathing NPR post-decongestant measurements, ITT population	Baseline			6 months			12 months		
	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)	Septoplasty (*N* = 188)	Medical management (*N* = 190)	Overall (*N* = 378)
ITT population, *n* (% of *N*)	151 (80)	155 (82)	306 (81)	126 (67)	123 (65)	249 (66)	66 (35)	72 (38)	138 (37)
Median (IQR)	0.3 (0.1–0.6)	0.3 (0.1–0.6)	0.3 (0.1–0.6)	0.1 (0.1–0.4)	0.3 (0.1–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.2 (0.1–0.5)	0.2 (0.1–0.4)
Mean (SD)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)
95% CI about mean	0.3 to 0.4	0.3 to 0.4	0.36 to 0.43	0.2 to 0.3	0.3 to 0.4	0.25 to 0.32	0.2 to 0.3	0.2 to 0.4	0.23 to 0.31
Minimum, maximum	0, 1	0, 1	0, 1	0, 0.9	0, 1	0, 1	0, 1	0, 1	0, 1

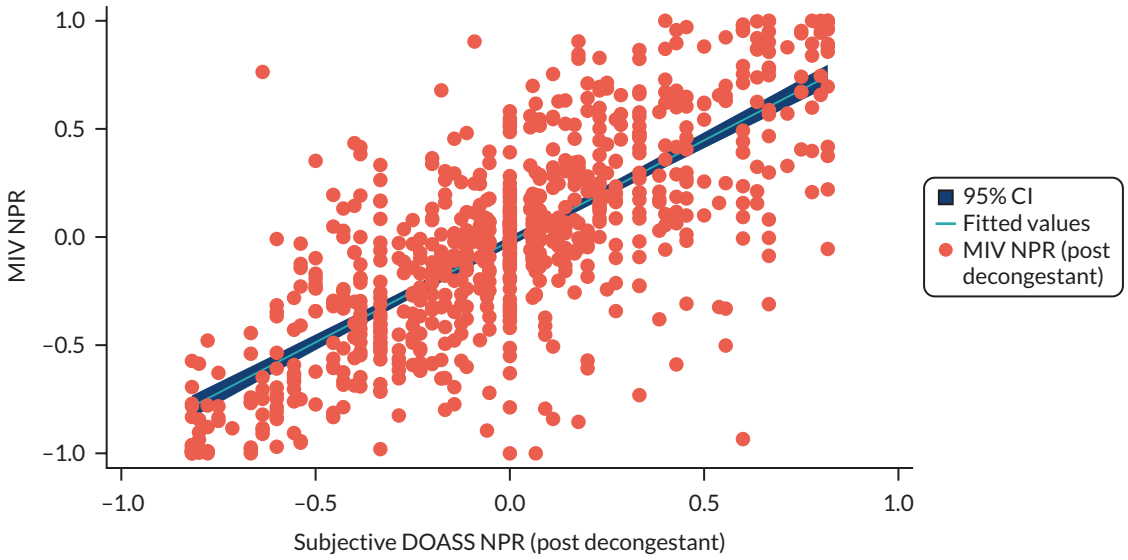

FIGURE 29 Subjective DOASS against MIV NPR (post decongestant, using mean volumes from three measurements).

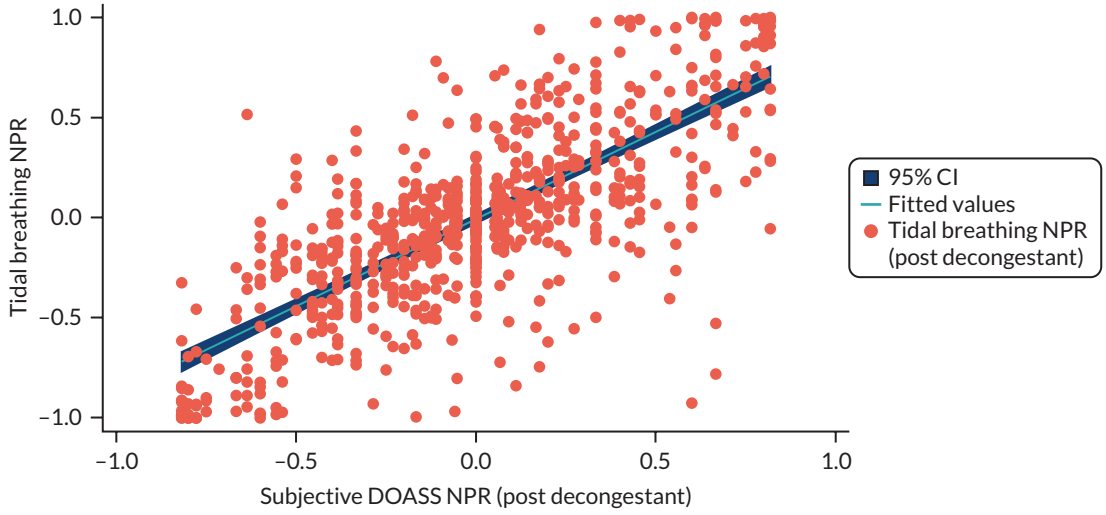

FIGURE 30 Subjective DOASS against tidal breathing NPR, post decongestant.

TABLE 57 Cross-tabulation of whether or not reduced turbinate was recommended and whether or not it was carried out, septoplasty arm only

	Turbinate, *n* (%)		
Recommendation	**Not reduced**	**Reduced**	**Total, *n* (%)**
Turbinate reduction recommended	30 (45)	78 (89)	108 (70)
Turbinate reduction not recommended	33 (49)	10 (11)	43 (28)
Not applicable	4 (6)	0 (0)	4 (3)
Total	67 (100)	88 (100)	155 (100)

Note
Data available for 155 out of 166 participants.

TABLE 58 Presence of turbinate reduction and baseline assessments among those undergoing surgery in the septoplasty arm

Turbinate reduction and baseline assessment	Septoplasty arm (*n*)
Turbinate not reduced in line with baseline assessment	30
Turbinate not reduced, opposing baseline assessment	33
Turbinate reduced in line with baseline assessment	78
Turbinate reduced, opposing baseline assessment	10
Turbinate not reduced; baseline assessment 'not applicable'	4
Turbinate reduced; baseline assessment 'not applicable'	0
Turbinate reduction information missing	11
Total	166

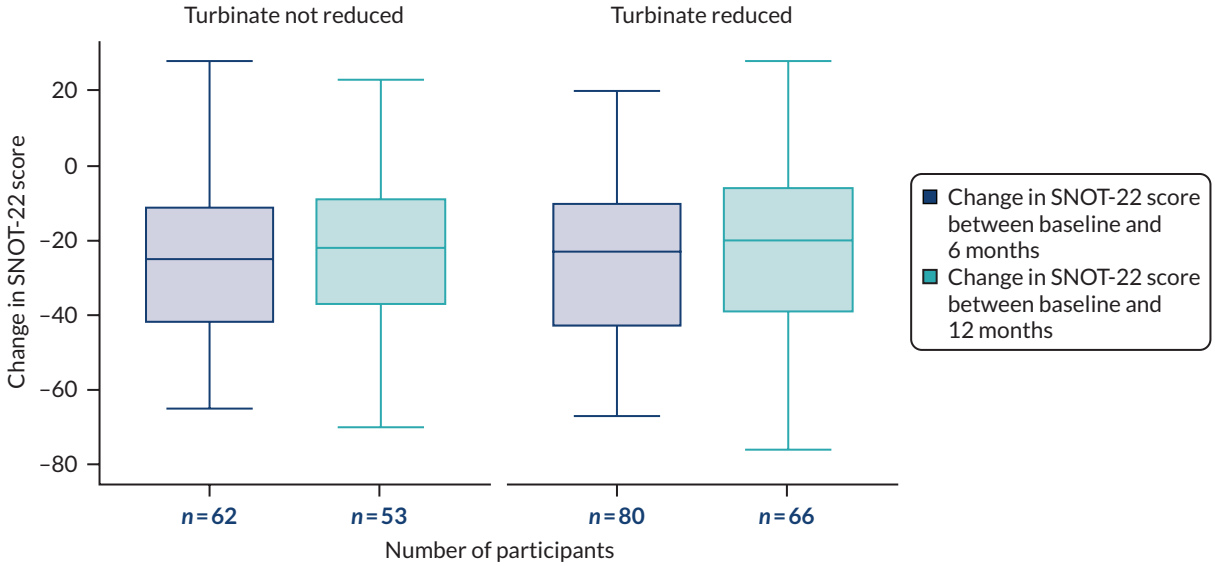

FIGURE 31 Relationship of turbinate reduction with SNOT-22 scores.

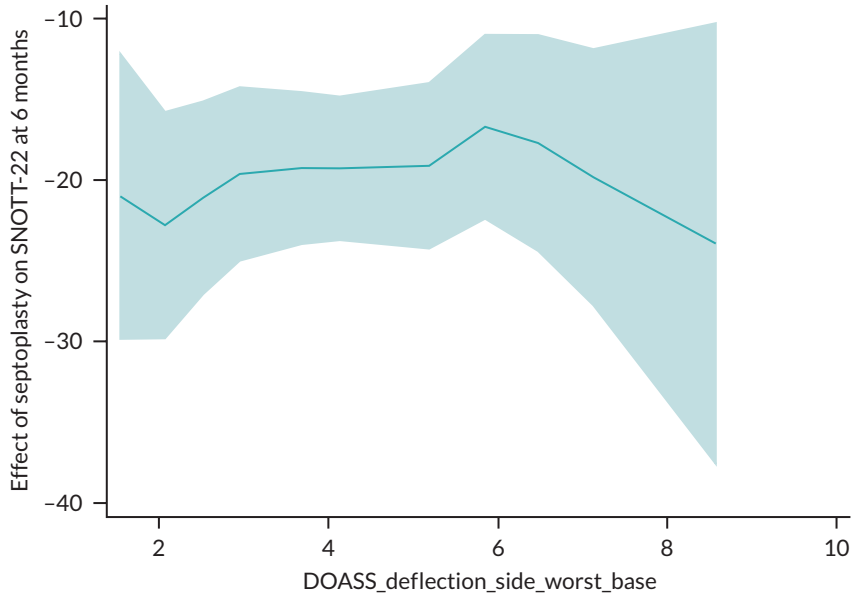

FIGURE 32 The STEPP of the SNOT-22 vs. the DOASS.

TABLE 59 Changes from baseline to time points: individual SNOT-22 scores by randomised arm and gender, ITT population

Category	Change from baseline to	
	6 months	12 months
Septoplasty, male		
N	100	76
Median (IQR)	−24.5 (−40.5 to −10)	−22.5 (−38.5 to −9)
Mean (SD)	−24.2 (20.7)	−23.7 (21.1)
95% CI	−28.3 to −20.1	−28.5 to −18.9
Minimum, maximum	−67, 28	−76, 28
Septoplasty, female		
n	52	43
Median (IQR)	−25 (−42 to −10)	−22 (−38 to −5)
Mean (SD)	−25.4 (20.0)	−22.0 (21.2)
95% CI	−31.0 to −19.8	−28.5 to −15.5
Minimum, maximum	−64, 12	−70, 27
Medical management, male		
n	99	79
Median (IQR)	−3 (−14 to 9)	−10 (−24 to 0)
Mean (SD)	−3.3 (17.6)	−11.0 (18.0)
95% CI	−6.8 to 0.2	−15.0 to −67.0
Minimum, maximum	−55, 38	−57, 36
Medical management, female		
n	56	46
Median (IQR)	−5.5 (−15.5 to −0.5)	−9 (−27 to −2)
Mean (SD)	−6.8 (14.7)	−14.3 (22.5)
95% CI	−10.7 to −2.8	−21.0 to −7.6
Minimum, maximum	−52, 27	−63, 40

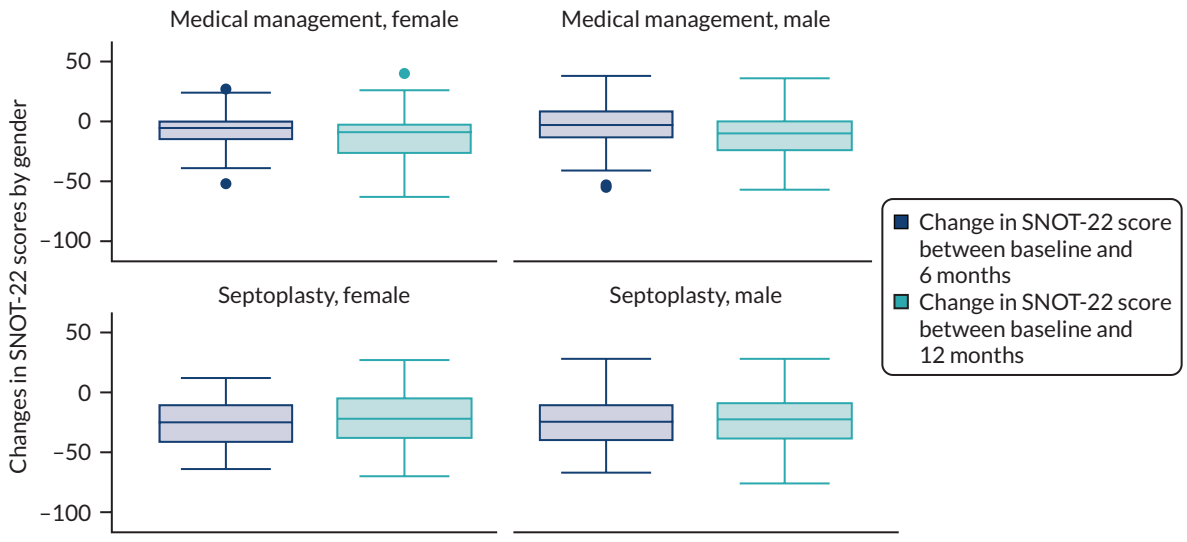

FIGURE 33 Changes in SNOT-22 scores by gender.

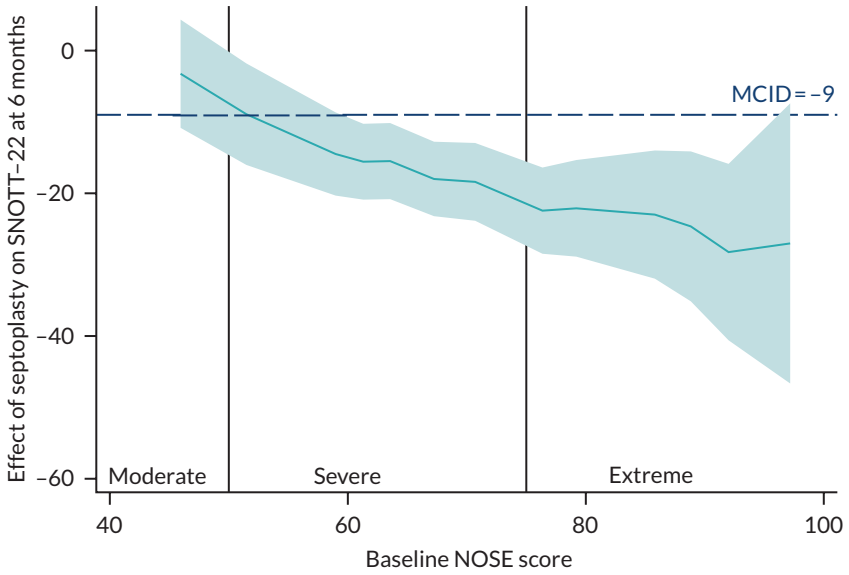

FIGURE 34 The STEPP of changes in SNOT-22 score by gender (male). *N* = 199: septoplasty, *n* = 100; medical management, *n* = 99.

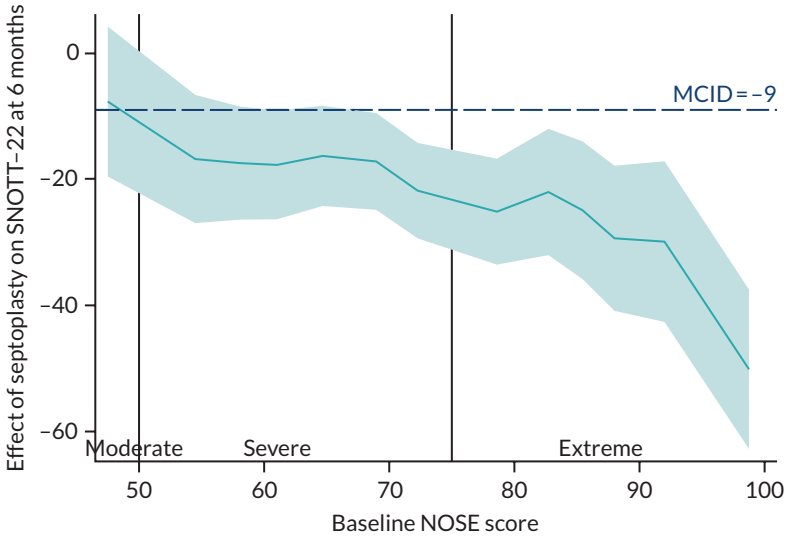

FIGURE 35 The STEPP of changes in SNOT-22 score by gender (female). *N* = 108: septoplasty, *n* = 52; medical management, *n* = 56.

TABLE 60 Severity grades of AEs by randomisation arm

AE	Trial arm (*n*)		Total (*N*)
	Septoplasty	Medical management	
Life-threatening	0	0	0
Severe	5	1	6
Moderate	39	22	61
Mild	88	72	160
Total	132	95	227

TABLE 61 Action taken to address reported AEs

Action taken	Trial arm, *n* (%)		Total, *N* (%)
	Septoplasty	Medical management	
No action taken	82 (63)	57 (59)	139 (61)
Treatment adjusted/interrupted	1 (< 1)	14 (14)	15 (7)
Treatment discontinued	0 (0)	8 (8)	8 (4)
Concomitant medications	45 (35)	18 (19)	63 (28)
Non-drug therapy given	2 (1)	0 (0)	2 (< 1)
Hospitalisation	0 (0)	0 (0)	0 (0)
Total	130 (100)	97 (100)	227 (100)

Notes
Two medical management participants had two actions taken for the same AE: treatment discontinued/adjusted/interrupted and concomitant medication given. Two septoplasty participants did not have any of the actions recorded.

TABLE 62 Status of reported AEs

Action taken	Trial arm, *n* (%)		Total, *N* (%)
	Septoplasty	Medical management	
Resolved	95 (72)	55 (58)	150 (66)
Resolving	14 (11)	5 (5)	19 (8)
Ongoing	23 (17)	35 (37)	58 (26)
Total	132 (100)	95 (100)	227 (100)

TABLE 63 Adverse event causality and severity

Related to treatment	Severity	Trial arm (*n*)	
		Septoplasty	Medical management
Definitely	Mild	19	5
	Moderate	6	0
	Severe	5	0
	Life-threatening	0	0
Probable	Mild	12	21
	Moderate	8	0
	Severe	0	0
	Life-threatening	0	0
Possible	Mild	24	9
	Moderate	11	8
	Severe	0	1
	Life-threatening	0	0
Unlikely	Mild	9	6
	Moderate	3	3
	Severe	0	0
	Life-threatening	0	0
Unrelated	Mild	23	31
	Moderate	10	11
	Severe	0	0
	Life-threatening	0	0
Not assessable	Mild	1	0
	Moderate	0	0
	Severe	0	0
	Life-threatening	0	0
Total		131[a]	95

a One moderate AE did not have causality entered into MACRO.

TABLE 64 Adverse events reported after the end of the 12-month follow-up period

Study ID	Randomised date	AE date	Start AE date	Stop AE date	Completion	Time randomised to AE start (weeks)
20020	8 May 2019	9 May 2020	9 May 2020		22 December 2020	52.42857
80003	23 April 2018	28 April 2019	28 April 2019		2 May 2019	52.85714
60002	29 June 2018	8 August 2019	8 August 2019	8 August 2019	13 February 2020	57.85714

ID, identifier.

TABLE 65 Reported AEs: missing start date

Study ID	Randomised date	AE date	Start AE date	Stop AE date	Completion
10008	29 March 2018				20 May 2019
80003	23 April 2018				20 November 2020
80007	24 May 2018				20 November 2020
80032	29 May 2019				20 November 2020
120004	2 November 2018				30 April 2019
170015	10 May 2019				20 November 2019

ID, identifier.

TABLE 66 Line listing of AEs (227), all participants

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Septoplasty	Nasal pain	Definitely	Severe	1	Concomitant medications	Resolved
Septoplasty	Uncontrollable minor haemorrhage	Definitely	Severe	5	Concomitant medications	Resolved
Septoplasty	Pain (nasal)	Definitely	Severe	6	Concomitant medications	Resolved
Septoplasty	Pain	Definitely	Severe	6	Concomitant medications	Resolved
Septoplasty	Nasal pain	Definitely	Severe	9	Concomitant medications	Resolved
Septoplasty	Nasal pain	Definitely	Moderate	2	Concomitant medications	Resolved
Septoplasty	Nasal pain	Definitely	Moderate	4	Concomitant medications	Resolved
Septoplasty	Blocked nose – bilateral	Definitely	Moderate	6	No action taken	Resolving
Septoplasty	Nasal pain	Definitely	Moderate	6	Concomitant medications	Resolved
Septoplasty	Pain	Definitely	Moderate	7	Concomitant medications	Resolved
Septoplasty	Nasal pain	Definitely	Moderate	9	Concomitant medications	Resolved
Septoplasty	Nasal pain	Definitely	Mild	2	No action taken	Resolved
Septoplasty	Postoperative pain	Definitely	Mild	3	No action taken	Resolved
Septoplasty	Nasal pain	Definitely	Mild	4	Concomitant medications	Resolved
Septoplasty	Postoperative facial pain	Definitely	Mild	5	No action taken	Resolved
Septoplasty	Nasal pain	Definitely	Mild	5	Concomitant medications	Resolved

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Septoplasty	Nasal pain	Definitely	Mild	5	Concomitant medications	Resolved
Septoplasty	Epistaxis (right nostril)	Definitely	Mild	6	No action taken	Resolved
Septoplasty	Minor nasal bleeding post operation	Definitely	Mild	6	No action taken	Resolved
Septoplasty	Numbness of upper teeth	Definitely	Mild	6	No action taken	Resolved
Septoplasty	Nasal pain	Definitely	Mild	6	Concomitant medications	Resolved
Septoplasty	Numbness in upper teeth	Definitely	Mild	7	No action taken	Resolving
Septoplasty	Pain (nasal)	Definitely	Mild	7	Concomitant medications	Resolved
Septoplasty	Pain	Definitely	Mild	8	Concomitant medications	Resolved
Septoplasty	Bleeding from right nostril	Definitely	Mild	9	No action taken	Resolved
Septoplasty	Bleeding from left nostril	Definitely	Mild	9	No action taken	Resolved
Septoplasty	Blood clot in right nostril	Definitely	Mild	9	Non-drug therapy given	Resolved
Septoplasty	Adhesion	Definitely	Mild	28	No action taken	Ongoing
Septoplasty	Perforation	Definitely	Mild	28	No action taken	Ongoing
Septoplasty	Septal perforation	Definitely	Mild	Missing	No action taken	Ongoing
Medical management	Nosebleeds	Definitely	Mild	0	No action taken	Resolving
Medical management	Pain and bleeding after 2 weeks	Definitely	Mild	2	Treatment discontinued	Resolved
Medical management	Nosebleeds	Definitely	Mild	2	No action taken	Resolved
Medical management	Intermittent nosebleeds	Definitely	Mild	18	Treatment discontinued	Resolved
Medical management	Postoperative nasal infection	Definitely	Mild	28	Concomitant medications	Resolved
Septoplasty	Nasal congestion	Probable	Moderate	4	No action taken	Resolved
Septoplasty	Nose infection	Probable	Moderate	5	No action taken	Resolved
Septoplasty	Sinusitis	Probable	Moderate	6	Concomitant medications	Resolved
Septoplasty	Dizziness on movement	Probable	Moderate	6	No action taken	Resolved
Septoplasty	Excessive nasal mucus	Probable	Moderate	6	No action taken	Resolved
Septoplasty	Painful nose	Probable	Moderate	6	Concomitant medications	Resolved
Septoplasty	Sinus infection	Probable	Moderate	10	Concomitant medications	Resolved
Septoplasty	Infection in both nostrils	Probable	Moderate	14	Concomitant medications	Resolved
Septoplasty	Discomfort at tip of nose when touching it	Probable	Mild	3	No action taken	Resolving

continued

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Septoplasty	Nasal congestion	Probable	Mild	6	No action taken	Ongoing
Septoplasty	Raw area on left septal wall	Probable	Mild	6	No action taken	Resolved
Septoplasty	Numbness of teeth	Probable	Mild	7	No action taken	Resolved
Septoplasty	Headaches	Probable	Mild	8	No action taken	Resolved
Septoplasty	2–3 days' postoperative pyrexia (38.0 °C)	Probable	Mild	8	No action taken	Resolved
Septoplasty	Nasal pain	Probable	Mild	8	No action taken	Resolved
Septoplasty	One episode of epistaxis lasting 30 minutes	Probable	Mild	8	No action taken	Resolved
Septoplasty	Nasal infection	Probable	Mild	9	No action taken	Resolved
Septoplasty	Infection requiring antibiotics	Probable	Mild	13	No action taken	Resolved
Septoplasty	Epistaxis (small amount)	Probable	Mild	14	No action taken	Resolved
Septoplasty	Pain	Probable	Mild	14	Concomitant medications	Resolved
Medical management	Patient c/o pain/irritation when administering medication. Goes away soon after	Probable	Mild	0	No action taken	Ongoing
Medical management	Patient experiencing congestion and a runny nose for approximately 30 minutes following administration of spray	Probable	Mild	0	No action taken	Resolved
Medical management	Runny nose for 5 minutes following administration	Probable	Mild	0	No action taken	Ongoing
Medical management	Nasal crusting	Probable	Mild	0	No action taken	Ongoing
Medical management	Patient experiencing a runny nose for approximately 5 minutes following administration of sprays	Probable	Mild	0	No action taken	Resolved
Medical management	Sore throat	Probable	Mild	0	No action taken	Resolved
Medical management	Epistaxis	Probable	Mild	0	No action taken	Ongoing
Medical management	Dryness to nasal passages	Probable	Mild	1	Treatment adjusted/ interrupted	Ongoing
Medical management	Nasal pain	Probable	Mild	1	Treatment adjusted/ interrupted	Ongoing
Medical management	Epistaxis	Probable	Mild	1	Treatment adjusted/ interrupted	Ongoing
Medical management	Nasal bleeding	Probable	Mild	1	No action taken	Resolved
Medical management	Bleed from left nostril when douching	Probable	Mild	1	No action taken	Ongoing

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Medical management	Pain	Probable	Mild	2	Treatment adjusted/ interrupted	Resolving
Medical management	Small amount of bleeding when blowing nose	Probable	Mild	2	Treatment adjusted/ interrupted	Resolving
Medical management	Bleed from both nostrils when douching	Probable	Mild	2	No action taken	Ongoing
Medical management	Dry nose	Probable	Mild	2	Treatment adjusted/ interrupted	Ongoing
Medical management	Nasal itching	Probable	Mild	4	Treatment adjusted/ interrupted	Ongoing
Medical management	Pain in nostrils	Probable	Mild	4	Treatment adjusted/ interrupted	Resolved
Medical management	Rash inside nose	Probable	Mild	4	Treatment adjusted/ interrupted	Ongoing
Medical management	Epistaxis	Probable	Mild	6	Treatment discontinued	Ongoing
Medical management	Rhinorrhoea	Probable	Mild	Missing	No action taken	Ongoing
Medical management	Fever	Possible	Severe	40	Concomitant medications	Resolved
Septoplasty	New burning sensation; feels like sinusitis	Possible	Moderate	5	No action taken	Ongoing
Septoplasty	Postoperative infection	Possible	Moderate	6	Concomitant medications	Resolving
Septoplasty	Loss of taste	Possible	Moderate	6	No action taken	Resolved
Septoplasty	Postoperative nasal infection	Possible	Moderate	7	No action taken	Resolved
Septoplasty	Runny nose	Possible	Moderate	8	Concomitant medications	Resolved
Septoplasty	Ear blocked	Possible	Moderate	8	No action taken	Resolved
Septoplasty	Postoperative nasal wound infection	Possible	Moderate	9	Concomitant medications	Resolved
Septoplasty	Right hypoglossal nerve palsy	Possible	Moderate	11	No action taken	Ongoing
Septoplasty	Postoperative infection	Possible	Moderate	12	Concomitant medications	Resolved
Septoplasty	Infection	Possible	Moderate	25	Concomitant medications	Resolved
Septoplasty	Revision septoplasty	Possible	Moderate	47	Non-drug therapy given	Ongoing
Medical management	Rhinorrhoea	Possible	Moderate	0	No action taken	Ongoing

continued

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Medical management	Sore throat	Possible	Moderate	3	Treatment adjusted/ interrupted	Resolved
Medical management	Nosebleeds associated with medication	Possible	Moderate	8	Treatment adjusted/ interrupted then discontinued	Resolved
Medical management	Epistaxis from left nostril	Possible	Moderate	14	No action taken	Resolved
Medical management	Headaches	Possible	Moderate	19	No action taken	Ongoing
Medical management	Bleeding from right nasal passage	Possible	Moderate	20	Treatment discontinued	Resolved
Medical management	Pain from right nasal passage	Possible	Moderate	20	Treatment discontinued	Resolved
Medical management	Infection requiring antibiotic treatment	Possible	Moderate	21	Concomitant medications	Resolved
Septoplasty	Mouth sores	Possible	Mild	4	No action taken	Resolved
Septoplasty	Headaches	Possible	Mild	4	Concomitant medications	Ongoing
Septoplasty	Expelling yellow mucus from both nostrils	Possible	Mild	4	No action taken	Resolved
Septoplasty	Sore throat	Possible	Mild	4	No action taken	Resolved
Septoplasty	Painful upper front teeth	Possible	Mild	5	No action taken	Resolving
Septoplasty	Brief drop in SATs	Possible	Mild	5	Unknown	Resolved
Septoplasty	Numb upper lip	Possible	Mild	5	No action taken	Resolving
Septoplasty	Patient states burning sensation to left nostril	Possible	Mild	5	No action taken	Resolved
Septoplasty	Clear discharge from left nostril	Possible	Mild	6	No action taken	Resolved
Septoplasty	Insomnia	Possible	Mild	6	Concomitant medications	Resolved
Septoplasty	Epistaxis	Possible	Mild	6	No action taken	Resolved
Septoplasty	Loss of sense of smell	Possible	Mild	6	No action taken	Resolved
Septoplasty	Infection	Possible	Mild	7	No action taken	Resolved
Septoplasty	Patient felt had infection as was producing large amount of mucus in nose	Possible	Mild	7	Concomitant medications	Resolved
Septoplasty	Raised temperature for 48 hours	Possible	Mild	8	Concomitant medications	Resolved
Septoplasty	Subjective asymmetry to nostrils	Possible	Mild	8	Unknown	Ongoing
Septoplasty	Nosebleeds	Possible	Mild	8	No action taken	Ongoing
Septoplasty	Nasal hypersensitivity to cold air	Possible	Mild	10	No action taken	Ongoing
Septoplasty	Swelling to the left side of the nose	Possible	Mild	13	No action taken	Resolved

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Septoplasty	Right nosebleed	Possible	Mild	15	Concomitant medications	Resolving
Septoplasty	Right nosebleed	Possible	Mild	24	Concomitant medications	Resolved
Septoplasty	Change of shape of nose	Possible	Mild	52	No action taken	Ongoing
Septoplasty	Bilateral alar battens with auricular cartilage graft	Possible	Mild	58	No action taken	Resolved
Septoplasty	Nasal congestion	Possible	Mild		Concomitant medications	Ongoing
Medical management	Slight blood on tissue after blowing nose	Possible	Mild	0	No action taken	Resolved
Medical management	Nasal pain	Possible	Mild	0	Concomitant medications	Resolved
Medical management	Irritation in top of mouth	Possible	Mild	0	No action taken	Resolving
Medical management	Nasal bleeding when blowing nose	Possible	Mild	0	No action taken	Ongoing
Medical management	Minor nosebleed (spotting) on a couple of occasions	Possible	Mild	0	No action taken	Resolved
Medical management	Headache	Possible	Mild	4	Concomitant medications	Resolved
Medical management	Nausea	Possible	Mild	6	Treatment discontinued	Ongoing
Medical management	Epistaxis	Possible	Mild	10	Treatment adjusted/ interrupted	Resolved
Medical management	Notices some dried blood on tissues when blowing nose. Advice given regarding application of nasal sprays	Possible	Mild	13	No action taken	Resolved
Septoplasty	Sore throat	Unlikely	Moderate	4	No action taken	Resolved
Septoplasty	Nausea	Unlikely	Moderate	11	No action taken	Ongoing
Septoplasty	Swelling in left side of nose and face, patient reported	Unlikely	Moderate	48	No action taken	Resolved
Medical management	Heartburn	Unlikely	Moderate	1	Treatment adjusted/ interrupted	Resolved
Medical management	Possible sinus infection and cough	Unlikely	Moderate	26	No action taken	Ongoing
Medical management	Complaining of heartburn	Unlikely	Moderate	32	No action taken	Ongoing
Septoplasty	Feels bones in fingers are sore	Unlikely	Mild	1	No action taken	Resolved
Septoplasty	Feels tired	Unlikely	Mild	1	No action taken	Resolved
Septoplasty	Tinnitus	Unlikely	Mild	5	No action taken	Resolving

continued

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Septoplasty	Increased mucus production	Unlikely	Mild	7	Concomitant medications	Resolved
Septoplasty	Sinus infection	Unlikely	Mild	9	Concomitant medications	Resolved
Septoplasty	Sinusitis	Unlikely	Mild	20	No action taken	Resolved
Septoplasty	Nasal congestion	Unlikely	Mild	20	No action taken	Ongoing
Septoplasty	Rhinitis	Unlikely	Mild	26	Concomitant medications	Ongoing
Septoplasty	Rhinitis	Unlikely	Mild	51	Concomitant medications	Ongoing
Medical management	Headache	Unlikely	Mild	0	Concomitant medications	Resolved
Medical management	Throat infection	Unlikely	Mild	1	Concomitant medications	Resolved
Medical management	Gastric reflux	Unlikely	Mild	2	Concomitant medications	Ongoing
Medical management	Urinary tract infection	Unlikely	Mild	5	Concomitant medications	Resolved
Medical management	Sinus infection	Unlikely	Mild	45	No action taken	Resolved
Medical management	Reduced liver enzymes	Unlikely	Mild	47	No action taken	Resolved
Septoplasty	Nasal pain – bridge of nose	Unrelated	Moderate	6	No action taken	Resolved
Septoplasty	Post-surgery nasal pain	Unrelated	Moderate	6	No action taken	Resolved
Septoplasty	Urinary tract infection	Unrelated	Moderate	7	No action taken	Resolved
Septoplasty	Cold symptoms	Unrelated	Moderate	7	No action taken	Resolved
Septoplasty	Wisdom tooth infection	Unrelated	Moderate	7	Concomitant medications	Resolved
Septoplasty	ECG changes post induction of anaesthesia. ST depression and T-wave inversion	Unrelated	Moderate	8	Treatment adjusted/ interrupted	Ongoing
Septoplasty	Nasal obstruction	Unrelated	Moderate	10	No action taken	Ongoing
Septoplasty	Sciatica	Unrelated	Moderate	17	Concomitant medications	Ongoing
Septoplasty	Influenza	Unrelated	Moderate	39	No action taken	Resolved
Septoplasty	Fractured wrist	Unrelated	Moderate	44	No action taken	Resolving
Medical management	Headache	Unrelated	Moderate	2	No action taken	Resolved
Medical management	Sore shoulder	Unrelated	Moderate	2	No action taken	Resolved
Medical management	Toothache due to a gum infection	Unrelated	Moderate	3	No action taken	Resolved
Medical management	Ablation for varicose veins	Unrelated	Moderate	6	No action taken	Resolved

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Medical management	Exacerbation of anxiety	Unrelated	Moderate	16	No action taken	Ongoing
Medical management	Diagnosis of fatty liver (non-acute)	Unrelated	Moderate	18	Treatment discontinued	Ongoing
Medical management	Asthma exacerbation	Unrelated	Moderate	19	Concomitant medications	Resolved
Medical management	Anxiety	Unrelated	Moderate	22	No action taken	Resolved
Medical management	Sinusitis	Unrelated	Moderate	24	No action taken	Resolved
Medical management	Subluxation of left shoulder	Unrelated	Moderate	29	No action taken	Ongoing
Medical management	Back pain	Unrelated	Moderate	43	No action taken	Resolving
Septoplasty	Post anaesthesia antibiotics given prophylactically because of splenectomy	Unrelated	Mild	6	No action taken	Resolved
Septoplasty	Kept in hospital overnight because of pre-existing condition; arranged at pre assessment	Unrelated	Mild	7	No action taken	Resolved
Septoplasty	Pulled muscle in hip	Unrelated	Mild	8	No action taken	Resolving
Septoplasty	Chest pain – sinus tachycardia on ECG	Unrelated	Mild	9	No action taken	Resolved
Septoplasty	Swollen lower lip	Unrelated	Mild	10	No action taken	Resolved
Septoplasty	Viral cold	Unrelated	Mild	14	Concomitant medications	Resolved
Septoplasty	Facial pain	Unrelated	Mild	14	No action taken	Ongoing
Septoplasty	Small fracture distal fibula	Unrelated	Mild	16	No action taken	Resolved
Septoplasty	Viral cold	Unrelated	Mild	19	Concomitant medications	Resolved
Septoplasty	Dental extraction	Unrelated	Mild	21	Concomitant medications	Resolved
Septoplasty	Dizziness – when moving head	Unrelated	Mild	22	No action taken	Ongoing
Septoplasty	Fungal ear infection	Unrelated	Mild	22	Concomitant medications	Resolved
Septoplasty	Mechanical fall causing bruising to nose. No nasal or facial fracture	Unrelated	Mild	23	No action taken	Resolved
Septoplasty	Viral cold	Unrelated	Mild	23	Concomitant medications	Resolving
Septoplasty	Rhinitis	Unrelated	Mild	24	No action taken	Resolved
Septoplasty	COVID-19	Unrelated	Mild	28	No action taken	Resolved
Septoplasty	Muscular chest pains	Unrelated	Mild	33	No action taken	Resolving
Septoplasty	Cough	Unrelated	Mild	39	No action taken	Resolved

continued

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Septoplasty	Type 2 diabetes	Unrelated	Mild	49	No action taken	Ongoing
Septoplasty	Labyrinthitis	Unrelated	Mild	49	Concomitant medications	Resolved
Septoplasty	Head collision with a cow. Bleeding nose, which is now swollen, and two black eyes	Unrelated	Mild	53	No action taken	Resolving
Septoplasty	Influenza-like symptoms and nasal congestion	Unrelated	Mild	Missing	No action taken	Resolved
Septoplasty	Cold	Unrelated	Mild	Missing	No action taken	Resolved
Medical management	Sinus infection	Unrelated	Mild	0	Concomitant medications	Resolved
Medical management	Common cold	Unrelated	Mild	1	No action taken	Resolved
Medical management	Depression	Unrelated	Mild	1	No action taken	Ongoing
Medical management	Viral head cold	Unrelated	Mild	1	No action taken	Resolved
Medical management	Influenza, as described by participant	Unrelated	Mild	1	Treatment adjusted/ interrupted and con medications	Resolved
Medical management	Headache	Unrelated	Mild	2	No action taken	Resolved
Medical management	Cold/influenza	Unrelated	Mild	3	Concomitant medications	Resolved
Medical management	Sinusitis	Unrelated	Mild	5	Concomitant medications	Ongoing
Medical management	Headaches	Unrelated	Mild	6	Concomitant medications	Ongoing
Medical management	Viral head cold	Unrelated	Mild	7	No action taken	Resolved
Medical management	Hip pain	Unrelated	Mild	11	No action taken	Resolved
Medical management	Bites to ankles	Unrelated	Mild	12	No action taken	Resolved
Medical management	Perianal infection	Unrelated	Mild	13	No action taken	Resolved
Medical management	Bleeding from the nose	Unrelated	Mild	17	No action taken	Resolved
Medical management	Arthritis in left hip	Unrelated	Mild	21	No action taken	Ongoing
Medical management	Diagnosis of type 2 diabetes	Unrelated	Mild	21	No action taken	Ongoing
Medical management	Epigastric pain	Unrelated	Mild	23	No action taken	Ongoing

TABLE 66 Line listing of AEs (227), all participants (*continued*)

Trial arm	AE	Related to treatment	Severity	Time from randomisation to AE (weeks)	Action taken	Outcome
Medical management	Back injury	Unrelated	Mild	25	No action taken	Ongoing
Medical management	Sinusitis	Unrelated	Mild	26	Concomitant medications	Resolved
Medical management	Vasovagal episode	Unrelated	Mild	27	No action taken	Resolved
Medical management	Hit in face by ball	Unrelated	Mild	31	No action taken	Resolved
Medical management	Muscular strain, right shoulder, following MVA	Unrelated	Mild	35	No action taken	Resolved
Medical management	Hypertension	Unrelated	Mild	36	Concomitant medications	Ongoing
Medical management	Vitamin D deficiency	Unrelated	Mild	37	No action taken	Resolved
Medical management	Heartburn	Unrelated	Mild	38	No action taken	Resolved
Medical management	Diagnosis of osteopenia	Unrelated	Mild	42	No action taken	Ongoing
Medical management	Chest infection	Unrelated	Mild	42	No action taken	Resolved
Medical management	Bladder infection	Unrelated	Mild	43	Concomitant medications	Resolved
Medical management	Nasal tip numbness	Unrelated	Mild	43	No action taken	Resolved
Medical management	Developed dermatitis	Unrelated	Mild	45	No action taken	Ongoing
Medical management	Right lower quadrant abdominal pain	Unrelated	Mild	Missing	No action taken	Ongoing
Septoplasty	Nasal infection	Missing	Moderate	10	No action taken	Resolved
Septoplasty	Rhinitis	Not assessable	Mild	50	No action taken	Resolving

ECG, electrocardiogram; MVA, motor vehicle accident; SAT, blood oxygen saturation levels.

Note
c/o, complaining of.

TABLE 67 Serious AE causality and severity

		Trial arm (*n*)	
Related to treatment	**Severity**	**Septoplasty**	**Medical management**
Definitely	Mild	5	0
	Moderate	1	0
	Severe	0	0
	Life-threatening	0	0
Probable	Mild	2	0
	Moderate	1	0
	Severe	0	0
	Life-threatening	0	0
Possible	Mild	0	0
	Moderate	1	0
	Severe	0	0
	Life-threatening	0	0
Unlikely	Mild	1	0
	Moderate	0	0
	Severe	0	0
	Life-threatening	0	0
Unrelated	Mild	2	1
	Moderate	1	5
	Severe	0	1
	Life-threatening	0	2
Total		14	9

TABLE 68 Serious AEs (most frequently reported)

SAE coded	Grade	Trial arm (*n*)		Total (*n*)
		Septoplasty	Medical management	
Unexpected events occurring during surgical intervention (e.g. excessive bleeding) (A)	Mild	0	0	0
	Moderate	0	1	1
	Severe	0	0	0
	Life-threatening	0	0	0
Significant postoperative bleeding, above that normally expected following the surgical intervention (B)	Mild	3	0	3
	Moderate	2	1	3
	Severe	0	0	0
	Life-threatening	0	0	0
Complications related to the administration of the general anaesthetic (C)	Mild	5	1	6
	Moderate	0	1	1
	Severe	0	1	1
	Life-threatening	0	0	0
Unexpected events related to septoplasty (D)	Mild	0	0	0
	Moderate	0	0	0
	Severe	0	0	0
	Life-threatening	0	0	0
Other (E)	Mild	2	0	2
	Moderate	2	2	4
	Severe	0	0	0
	Life-threatening	0	2	2
Total		14	9	23

Note
The codes (A) to (E) show how the SAEs reported in this table can be linked to the full SAE line listing in *Table 69*.

TABLE 69 Line listing of all reported SAEs (*n* = 23)

Trial arm	SAE (codes in parentheses are listed *Table 68*)	Related to treatment	Severity	Time in weeks from randomisation to SAE	Action taken	Outcome	SUSAR
Septoplasty	Postoperative epistaxis with possible infection (B)	Definitely	Moderate	7	Hospitalisation	Resolved	
Septoplasty	Postoperative epistaxis (B)	Definitely	Mild	5	Hospitalisation	Resolved	Yes
Septoplasty	Vasovagal (C)	Definitely	Mild	5	Hospitalisation	Resolved	
Septoplasty	Shortness of breath, anxiety (C)	Definitely	Mild	6	Hospitalisation	Resolved	Yes
Septoplasty	Nasal bleeding post operation (B)	Definitely	Mild	9	Hospitalisation	Resolved	

continued

TABLE 69 Line listing of all reported SAEs (*n* = 23) (*continued*)

Trial arm	SAE (codes in parentheses are listed *Table 68*)	Related to treatment	Severity	Time in weeks from randomisation to SAE	Action taken	Outcome	SUSAR
Septoplasty	Postoperative oxygen desaturation (C)	Definitely	Mild	10	Hospitalisation	Resolved	Yes
Medical management	Unwell post operatively (C)	Definitely	Mild	29	Hospitalisation	Resolved	
Septoplasty	Re-admission owing to infection (E)	Probable	Moderate	7	Hospitalisation	Resolved	
Septoplasty	Chest pain (C)	Probable	Mild	4	Hospitalisation	Resolved	Yes
Septoplasty	Admitted with epistaxis from septal perforation (B)	Probable	Mild	32	Hospitalisation	Resolved	
Septoplasty	Post-septoplasty haemorrhage (B)	Possible	Moderate	7	Hospitalisation	Resolved	
Septoplasty	Drop in blood pressure necessitating overnight stay (C)	Unlikely	Mild	6	Hospitalisation	Resolved	
Medical management	Traumatic abdominal injury (E)	Unrelated	Life-threatening	3	Hospitalisation	Resolving	
Medical management	Polypharmacy overdose (E)	Unrelated	Life-threatening	48	Hospitalisation	Resolved	
Medical management	Respiratory, thoracic and mediastinal disorders (pneumonia) (C)	Unrelated	Severe	16	Hospitalisation	Resolved	
Medical management	Polypharmacy overdose (E)	Unrelated	Moderate	14	Hospitalisation	Resolved	
Septoplasty	Viral infection (E)	Unrelated	Moderate	22	Concomitant medications	Resolved	
Medical management	Polypharmacy overdose (E)	Unrelated	Moderate	23	Hospitalisation	Resolved	
Medical management	Chest tightness (C)	Unrelated	Moderate	26	Hospitalisation	Resolved	
Medical management	Postoperative bleed (B)	Unrelated	Moderate	34	Hospitalisation	Resolved	
Medical management	Postoperative infection with drifting of nasal septum (A)	Unrelated	Moderate	36	Hospitalisation	Ongoing	
Septoplasty	Inappropriate admission (E)	Unrelated	Mild	6	Hospitalisation	Resolved	
Septoplasty	Did not meet criteria for day-case surgery (E)	Unrelated	Mild	10	Hospitalisation	Resolved	

Note
Of the SAEs, 22 (96%) resulted in hospitalisation; the other was treated with concomitant medication; 21 (91%) SAEs were resolved by end of trial, one was categorised as resolving and one was ongoing.
SUSAR, suspected unexpected serious adverse reactions.

TABLE 70 Recategorisation of 'other surgery complications'

Original text	Recategorised by clinical team
Had overnight stay in hospital as he was given a hot cup of tea to drink post op[eration] and then had nasal bleeding. Discharged home the next day	Bleeding
Severe nasal bleeding and blocked nose, attended A[&]E – nose packed	Bleeding
Was given antibiotics by GP but no symptoms or findings suggestive of infection so NO infection confirmed	Infection
Chest pain	Other
Clinic 9 April 2019 with concern regarding nasal support, but feels this has settled now and is happy	Other
Inflammation secondary to splint – Naseptin[®, Alliance Pharmaceuticals plc, Chippenham, UK] given	Other
Upper front teeth painful and upper lip numb	Other
Rhinitis more noticeable	Other
Left nasal valve collapse. Improvement of left anterior septal deviation	Other
Nasal tip numbness	Other
Small polyp arising right middle turbinate. Had polyps many years ago. Will review at 12 months	Remove not a complication
Sense of smell improved	Remove not a complication
Patient still feels a little bit of pain and is uncomfortable; however, symptoms decreased and feel much better	Remove not a complication
Questionnaires by post. No info[rmation] on numbness, teeth, change in appearance of nose. SNOT-22 ticked to say sense of smell mild pre, and moderate post, surgery	Remove not a complication
Unable to complete at this time as surgery carried out after 6-month assessment. Will assess at 2-week follow-up phone call	Remove not a complication
P[atien]t asymptomatic, has L[eft] mild anterior septal deviation	Remove not a complication
Two stitches have come out	Remove not a complication
Unable to contact; patient not answering telephone	Remove not a complication
Nasal pain requiring tramadol	Remove not a complication

BOX 1 Line listing of other complications[a]

Chest pain.

Clinic 9 April 2019 with concern regarding nasal support, but feels this has settled now and is happy.

Inflammation secondary to splint – Naseptin given.

Upper front teeth painful and upper lip numb.

Rhinitis more noticeable.

Left nasal valve collapse. Improvement of left anterior septal deviation.

Nasal tip numbness.

a Line listings not covered in *Table 70*. Edited by clinical team to remove non-complication text (*n* = 7).

Appendix 2 Additional health economic analysis

TABLE 71 Unit costs

Resource use	Unit cost (£)	Source	Notes
GP consultation	34.00	PSSRU 2020[103]	
Practice nurse consultation	10.50	PSSRU 2020,[103] PSSRU 2015[190]	Assumed to be a 15-minute consultation
Nurse telephone consultation	4.20	PSSRU 2020,[103] PSSRU 2015[190]	Assumed to be a 6-minute consultation
GP telephone consultation	8.00	PSSRU 2020[103]	
NHS 111/NHS 24	15.05	PSSRU 2020[103]	GP-led triage
GP home visit	49.02	PSSRU 2020,[103] PSSRU 2015[190]	Assumed to be an 11.4-minute consultation
Nurse home visit	17.50	PSSRU 2020,[103] PSSRU 2015[190]	Assumed to be a 25-minute consultation
A&E visit	182	NHS reference costs 2019/20[105]	
Outpatient visit	147	NHS reference costs 2019/20[105]	
ENT outpatient visit	112	NHS reference costs 2019/20[105]	
Hospital admission (inpatient or day patient)	378	NHS reference costs 2019/20[105]	Assumed to be regular day/night admission
Septoplasty	1956	NHS reference costs 2019/20[105]	Day-case procedure
Time away from work			
Paid work day rate	134.40	ONS	
Time and travel costs			
Total inpatient time and travel cost	52.62	Time and travel questionnaire	
Total outpatient time and travel cost	44.65	Time and travel questionnaire	
Total GP time and travel cost	15.81	Time and travel questionnaire	

ONS, Office for National Statistics.

TABLE 72 Septoplasty unit costs: microcosting

Resource use	Unit cost (£)	Source
Theatre cost (per minute)	13.75	
Ward cost (total recovery time)	60.00	
Pre-assessment cost	9.50	
Consultant (per minute)	1.90	
Registrar (per minute)	0.83	
Scrub nurse (per minute)	0.83	
Operating department practitioner (per minute)	0.67	
Healthcare assistant (per minute)	0.23	
Anaesthetist assistant (per min)	0.67	
Septoplasty tray (cost per use)	5.37	Assumed 10-year lifespan, 3.5% discount for equivalent annual cost and used on average once per week
Septoplasty tray (autoclave)	40.00	
Anaesthetic consumables	46.15	
Surgical consumable	7.14	
Gowns – TSSU	2.00	

TSSU, Theatre Sterile Supply Unit.

TABLE 73 Response rates to participant questionnaires

Costs	Trial arm, *n* (%)	
	Medical management (*N* = 155)	Septoplasty (*N* = 152)
HUQ		
6 months	142 (92)	140 (92)
12 months	115 (74)	99 (65)
6 and 12 months	109 (70)	95 (63)
QALYs: SF-36		
Baseline	152 (98)	149 (98)
6 months	140 (90)	140 (92)
12 months	117 (75)	103 (68)
Baseline and 6 and 12 months	111 (72)	99 (65)

TABLE 74 Healthcare resource use

Resource	Medical management (*N* = 155)		Septoplasty (*N* = 152)	
	Mean (SD)	*n*	Mean (SD)	*n*
6 months				
Hospital admission	0.06 (0.23)	142	0.08 (0.27)	140
Number of days admitted	0.21 (1.28)	142	0.09 (0.31)	140
A&E visit	0.12 (0.33)	142	0.11 (0.31)	140
Number of A&E visits	0.17 (0.55)	142	0.12 (0.37)	140
ENT outpatient visit	0.18 (0.38)	142	0.38 (0.49)	140
Number of ENT outpatient visits	0.25 (0.65)	141	0.63 (1.01)	140
Outpatient visit	0.18 (0.39)	142	0.18 (0.38)	140
Number of outpatient visits	0.55 (2.72)	142	0.36 (0.98)	140
Face-to-face consultations	0.46 (0.50)	142	0.53 (0.50)	140
GP consultation	0.41 (0.49)	142	0.44 (0.50)	140
Number of GP consultations	0.88 (1.72)	142	0.92 (1.40)	140
Nurse consultation	0.19 (0.39)	142	0.17 (0.38)	140
Number of nurse consultations	0.25 (0.62)	142	0.29 (0.72)	140
Other consultations	0.09 (0.29)	142	0.14 (0.34)	140
Number of other consultations	0.33 (1.87)	142	0.23 (0.63)	140
Home consultations	0.01 (0.12)	142	0.00 (0.00)	140
GP consultation – home	0.01 (0.08)	142	0.00 (0.00)	140
Number of GP consultations – home	0.02 (0.25)	142	0.00 (0.00)	140
Nurse consultation – home	0.00 (0.00)	142	0.00 (0.00)	140
Number of nurse consultations – home	0.00 (0.00)	142	0.00 (0.00)	140
Other consultations – home	0.01 (0.08)	142	0.00 (0.00)	140
Number of other consultations – home	0.01 (0.17)	142	0.00 (0.00)	140
Telephone consultations	0.19 (0.39)	142	0.15 (0.36)	139
GP consultation – telephone	0.11 (0.31)	142	0.06 (0.25)	139
Number of GP consultations – telephone	0.16 (0.53)	142	0.12 (0.51)	139
Nurse consultation – telephone	0.04 (0.18)	142	0.03 (0.17)	139
Number of nurse consultations – telephone	0.04 (0.23)	142	0.06 (0.38)	139
NHS 111 consultation	0.04 (0.20)	142	0.02 (0.15)	139
Number of NHS 111 consultations	0.04 (0.20)	142	0.03 (0.21)	139
Other consultations – telephone	0.02 (0.14)	142	0.04 (0.19)	139
Number of other consultations – telephone	0.02 (0.15)	130	0.05 (0.25)	139
Private health care	0.04 (0.19)	140	0.01 (0.12)	138
Days off work	4.37 (11.55)	137	5.46 (8.77)	133

continued

TABLE 74 Healthcare resource use (*continued*)

Resource	Medical management (*N* = 155)		Septoplasty (*N* = 152)	
	Mean (SD)	*n*	Mean (SD)	*n*
12 months				
Hospital admission	0.05 (0.22)	115	0.00 (0.00)	99
Number of days admitted	0.09 (0.51)	115	0.00 (0.00)	99
A&E visit	0.11 (0.31)	114	0.09 (0.29)	99
Number of A&E visits	0.13 (0.43)	114	0.09 (0.29)	99
ENT outpatient visit	0.38 (0.49)	114	0.18 (0.39)	99
Number of ENT outpatient visits	0.69 (1.11)	113	0.25 (0.64)	99
Outpatient visit	0.21 (0.41)	114	0.19 (0.40)	99
Number of outpatient visits	0.32 (0.79)	114	0.32 (073)	99
Face-to-face consultations	0.50 (0.50)	115	0.45 (0.50)	99
GP consultation	0.34 (0.48)	115	0.35 (0.48)	99
Number of GP consultations	0.61 (1.18)	114	0.80 (1.48)	99
Nurse consultation	0.18 (0.39)	115	0.18 (0.39)	99
Number of nurse consultations	0.25 (0.59)	115	0.25 (0.59)	99
Other consultations	0.15 (0.36)	115	0.08 (0.27)	99
Number of other consultations	0.60 (3.32)	114	0.15 (0.61)	99
Home consultations	0.03 (0.16)	115	0.02 (0.14)	99
GP consultation – home	0.01 (0.09)	115	0.01 (0.10)	99
Number of GP consultations – home	0.01 (0.09)	115	0.01 (0.10)	99
Nurse consultation – home	0.01 (0.09)	115	0.00 (0.00)	99
Number of nurse consultations – home	0.01 (0.09)	115	0.00 (0.00)	99
Other consultations – home	0.00 (0.00)	115	0.01 (0.10)	99
Number of other consultations – home	0.00 (0.00)	115	0.05 (0.50)	99
Telephone consultations	0.28 (0.45)	115	0.20 (0.40)	99
GP consultation – telephone	0.19 (0.40)	115	0.10 (0.30)	99
Number of GP consultations – telephone	0.22 (0.55)	112	0.17 (0.62)	99
Nurse consultation – telephone	0.07 (0.26)	115	0.02 (0.14)	99
Number of nurse consultations – telephone	0.09 (0.39)	114	0.04 (0.28)	99
NHS 111 consultation	0.02 (0.13)	115	0.02 (0.14)	99
Number of NHS 111 consultations	0.01 (0.09)	114	0.02 (0.14)	99
Other consultations – telephone	0.06 (0.24)	115	0.09 (0.29)	99
Number of other consultations – telephone	0.08 (0.34)	110	0.12 (0.38)	95
Private health care	0.02 (0.13)	113	0.03 (0.17)	98
Days off work	4.62 (11.84)	111	2.23 (9.42)	94

TABLE 75 Number of concomitant medications reported

Medication name	Frequency
Aciclovir	2
Adcal	1
Alendronic acid	1
Amiloride hydrochloride	1
Amitriptyline	8
Amlodipine	5
Amoxicillin	16
Aspirin	2
Atenolol	1
Atorvastatin	7
Augmentin	1
Avamys nasal spray	3
Azithromycin	1
Baclofen	1
Bactroban nasal cream	6
Beclometasone	6
Beconase nasal spray	1
Becotide	1
Benadryl	1
Betamethasone	5
Bisoprolol	1
Candesartan	2
Cannabis oil	2
Carbamazepine	1
Carbocisteine	1
Cephalexin	2
Cerelle	1
Cetirizine	6
Charcoal	1
Chlorhexidine hydrochloride	1
Chlorphenamine	1
Citalopram	4
Clarithromycin	6
Clindamycin	1
Clopidogrel	2
Co-amoxiclav	21
Co-codamol	11

continued

TABLE 75 Number of concomitant medications reported (*continued*)

Medication name	Frequency
Codeine	5
Contraceptive pill	1
Creon	1
Cyclizine	2
Dermovate	1
Diazepam	2
Dihydrocodeine	5
Doxycycline	9
Duloxetine	3
Dymista® nasal spray (Meda AB, Solna, Sweden)	5
ECG	2
Elleste Solo™ patches (Meda AB)	2
EpiPen® (Mylan UK Healthcare Limited, Potters Bar, UK)	1
Erythromycin	1
Escitalopram	2
Esomeprazole	2
Estradiol	1
Fexofenadine	5
Flixonase	1
Flucloxacillin	6
Fluoxetine	4
Fluticasone	5
Folic acid	1
Furosemide	2
Gabapentin	4
Gaviscon (Reckitt Benckiser Group plc, Slough, UK)	1
Hydrocortisone	1
Ibuleve gel	1
Ibuprofen	20
Imigran	1
Ipratropium bromide	3
Irbesartan	1
Iv fluids	1
Lamotrigine	4
Lansoprazole	7
Lantus pen	1
Laxido	1
Lemsip	2

TABLE 75 Number of concomitant medications reported (*continued*)

Medication name	Frequency
Levothyroxine	4
Lisinopril	2
Lithium	1
Loestrin	1
Loperamide	1
Loratadine	5
Lorazepam	2
Macrobid	1
Mebeverine	1
Metformin	1
Methotrexate	1
Microgynon	1
Migraleve	1
Mirabegron	2
Mirtazapine	3
Mometasone nasal spray	13
Montelukast	1
Multivitamin	1
Naproxen	5
Nasal douche	8
Naseptin cream	15
Nasonex nasal spray	13
Neilmed sinus rinse	12
Neomycin sulfate	1
Nitrofurantoin	2
Nova pen	1
Novorapid	1
Oestrogen gel	1
Olanzapine	1
Omega 3	1
Omeprazole	13
Otomize spray	1
Otrivine nasal spray	2
Oxygen	1
Oxytetracycline	1
Pantoprazole	1
Paracetamol	35

continued

TABLE 75 Number of concomitant medications reported (*continued*)

Medication name	Frequency
Paroxetine	1
Penicillin	3
Pirinase	1
Piriton	1
Pramipexole	1
Prednisolone	2
Pregabalin	4
Progesterone	1
Propranolol	5
Quetiapine	3
Radiography	2
Ramipril	5
Ranitidine	1
Rigevidon	1
Roaccutane	1
Rosuvastatin	1
Salbutamol	8
Saline nasal spray	1
Senna	1
Seretide	1
Sertraline	7
Sildenafil	1
Silver nitrate	1
Sodium chloride	2
Stérimar nasal spray	14
Sudafed® nasal spray (Johnson & Johnson, Brunswick, NJ, USA)	1
Symbicort	1
Tadalafil	1
Tamsulosin	3
Tapentadol	1
Thyroxine	1
Tiotropium	1
Tizanidine hydrochloride	1
Tolterodine	1
Topiramate	1
Tramadol	4
Tranexamic acid	5
Troponin	2

TABLE 75 Number of concomitant medications reported (*continued*)

Medication name	Frequency
Uniphyllin	1
Varenicline	2
Venlafaxine	2
Ventolin	3
Vitamin B	1
Vitamin D	5
Ventilation/perfusion lung scan	1
Xylometazoline hydrochloride	1
Zimovane	1
Zolpidem	1
Zopiclone	1
Zydol	1

TABLE 76 Self-reported private health care

Resource used	Frequency
6 months	
Bupa (London, UK)	2
GP in Tunisia	1
Microsuction	1
Therapy	1
Physiotherapy to knee	1
Ealing Luxmedica	1
12 months	
ENT consultation	1
Osteopath	2
Physiotherapy	2
Therapist	1

TABLE 77 Time and travel data

Resource use	*n*	Mean (SD)
Hospital admissions		
Travel		
Car	116	0.72 (0.45)
Car miles	78	15.00 (16.15)
Car time (minutes)	78	31.05 (23.66)
Car parking costs (£)	68	2.20 (2.49)
Taxi	116	0.09 (0.28)
Taxi time (minutes)	10	15.80 (8.74)
Taxi fare (£)	10	7.71 (2.64)
Public transport	116	0.07 (0.25)
Public transport time (minutes)	8	22.63 (10.88)
Public transport fare (£)	8	1.65 (1.53)
Walking	116	0.02 (0.13)
Walking time (minutes)	2	10 (7.07)
Cost (£)	2	0.00 (0.00)
Total participant travel cost (£)	116	12.01 (13.61)
Total participant travel time (minutes)	116	24.23 (22.73)
Activity if not at appointment		
Paid work	110	0.70 (0.46)
Other	110	0.30 (0.46)
Total participant travel time cost (£)	116	10.88 (12.09)
Carer	116	0.53 (0.50)
Time waiting at hospital (minutes)	62	223.31 (227.65)
Activity if not at appointment		
Paid work	66	0.61 (0.49)
Other	66	0.39 (0.49)
Time cost travel and waiting (£)	56	60.94 (61.61)
Travel cost (£)	61	0.60 (1.96)
Total time and travel cost for a hospital admission	116	52.62 (63.41)
Hospital appointments		
Travel		
Car	185	0.86 (0.34)
Car miles	154	11.49 (12.50)
Car time (minutes)	153	24.73 (18.25)
Car parking costs (£)	145	1.29 (1.66)
Taxi	185	0.01 (0.10)
Taxi time (minutes)	2	20.00 (0.00)
Taxi fare (£)	2	9.50 (0.71)
Public transport	185	0.08 (0.27)
Public transport time (minutes)	13	39.46 (29.60)
Public transport fare (£)	11	2.89 (3.86)

TABLE 77 Time and travel data (*continued*)

Resource use	*n*	Mean (SD)
Walking	185	0.02 (0.15)
Walking time (minutes)	4	18.75 (13.77)
Cost (£)	4	0.00 (0.00)
Total participant travel cost (£)	185	10.79 (11.20)
Total participant travel time (mins)	185	25.13 (19.14)
Activity if not at appointment		
Paid work	159	0.77 (0.42)
Other	159	0.23 (0.42)
Total participant travel time cost (£)	185	10.37 (0.69)
Time waiting (minutes)	171	84.47 (93.45)
Total participant waiting time cost (£)	155	20.28 (27.66)
Carer	180	0.22 (0.41)
Activity if not at appointment		
Paid work	40	0.53 (0.51)
Other	40	0.47 (0.51)
Time cost travel and waiting (£)	32	33.29 (40.05)
Travel cost (£)	17	1.28 (3.38)
Total time and travel cost for a hospital appointment	185	44.65 (50.49)
GP appointments		
Travel		
Car	142	0.59 (0.49)
Car miles	82	5.19 (8.69)
Car time (minutes)	83	12.90 (12.80)
Car parking costs (£)	78	0.45 (1.32)
Taxi	142	0.04 (0.18)
Taxi time (minutes)	4	11.25 (6.29)
Taxi fare (£)	4	9.13 (6.41)
Public transport	142	0.08 (0.27)
Public transport time (minutes)	11	16.82 (9.56)
Public transport fare (£)	9	1.61 (1.81)
Walking	142	0.15 (0.36)
Walking time (minutes)	18	11.39 (6.55)
Cost (£)	16	0.00 (0.00)
Total participant travel cost (£)	142	3.66 (7.43)
Total participant travel time (mins)	142	10.62 (11.59)
Activity if not at appointment		
Paid work	112	0.72 (0.45)
Other	112	0.28 (0.45)
Total participant travel time cost (£)	142	4.29 (6.42)
Time waiting (minutes)	135	36.33 (35.12)
Total participant waiting time cost (£)	110	8.74 (10.07)

continued

TABLE 77 Time and travel data (*continued*)

Resource use	*n*	Mean (SD)
Carer	139	0.09 (0.29)
Activity if not at appointment		
Paid work	15	0.40 (0.51)
Other	15	0.60 (0.51)
Time cost travel and waiting (£)	9	9.70 (5.64)
Travel cost (£)	6	0.00 (0.00)
Total time and travel cost for a GP visit	142	15.81 (19.36)

n, number of participants who responded.

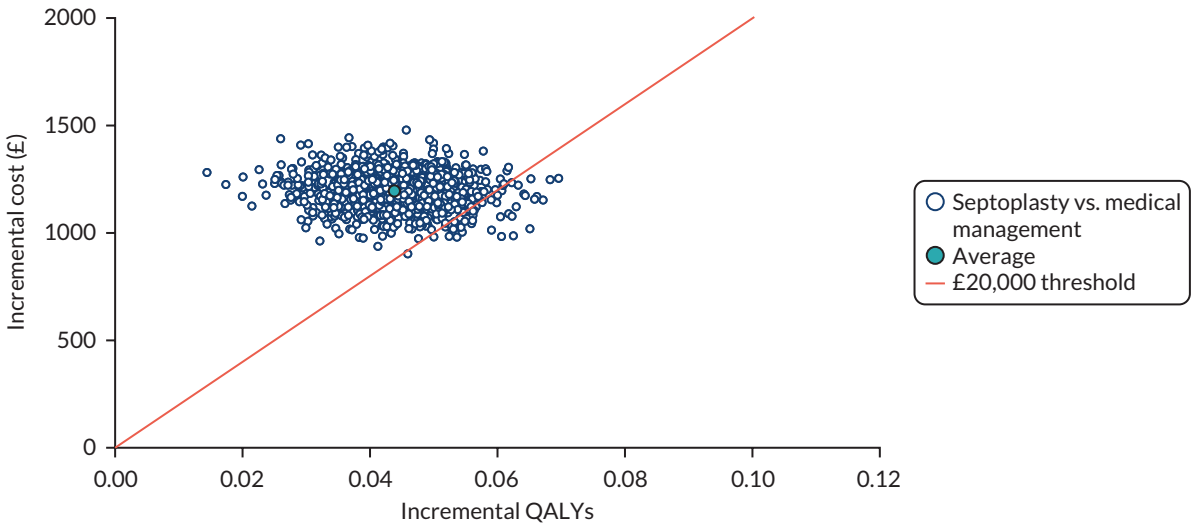

FIGURE 36 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CUA multiple imputation results.

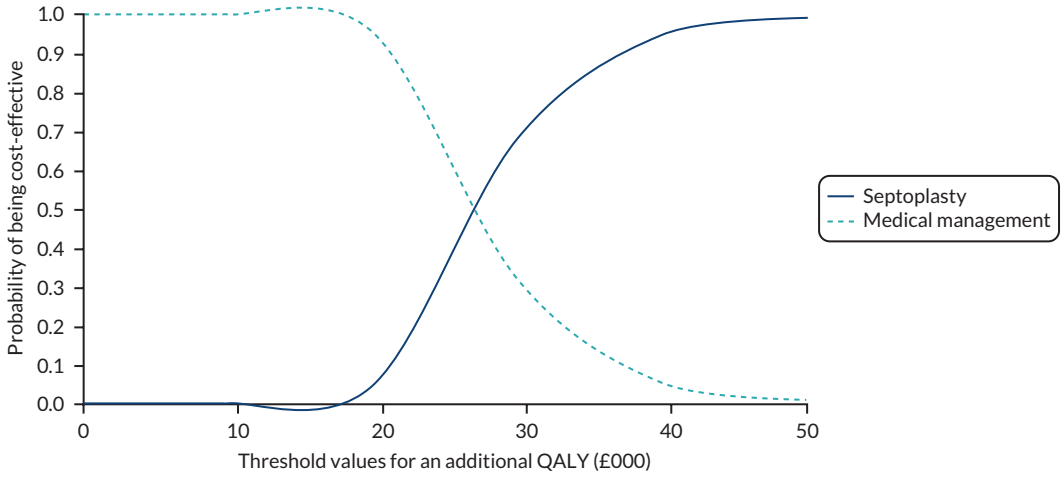

FIGURE 37 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CUA multiple imputation results.

TABLE 78 Cost-effectiveness acceptability sensitivity analysis: costs and SNOT-22 scores estimated at 6 months

Investigation strategy	Cost (95% CI)[a] (£)	Incremental cost (95% CI)[b] (£)	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an improvement in SNOT-22 scores				
						£0	£500	£1000	£3000	£5000
Outcome: SNOT-22 score at 6 months – results										
Medical management (costs, *n* = 142; outcomes, *n* = 155)	294 (216 to 372)	1790 (1698 to 1882)	0.381 (0.30 to 0.46)	0.416 (0.32 to 0.51)	4303	1.00	1.00	1.00	1.00	0.13
Septoplasty (costs, *n* = 140; outcomes, *n* = 152)	2071 (2016 to 2125)		0.803 (0.74 to 0.87)			0.00	0.00	0.00	0.00	0.87

a Point estimates are based on the unadjusted analysis (costs, *n* = 282; effects, *n* = 307).
b Incremental estimates are based on the adjusted analysis (*n* = 274); missing cost data were not imputed.

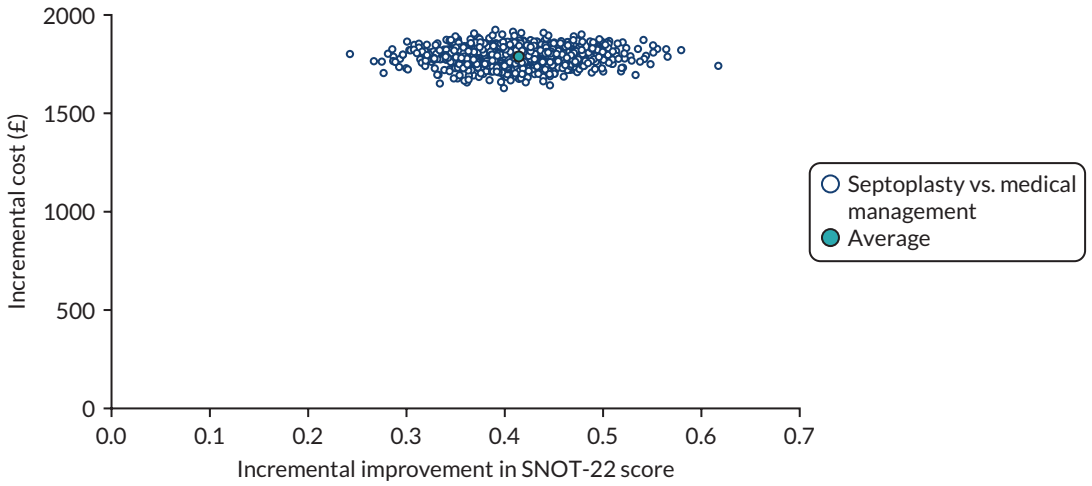

FIGURE 38 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CEA sensitivity analysis (costs and SNOT-22 scores estimated at 6 months).

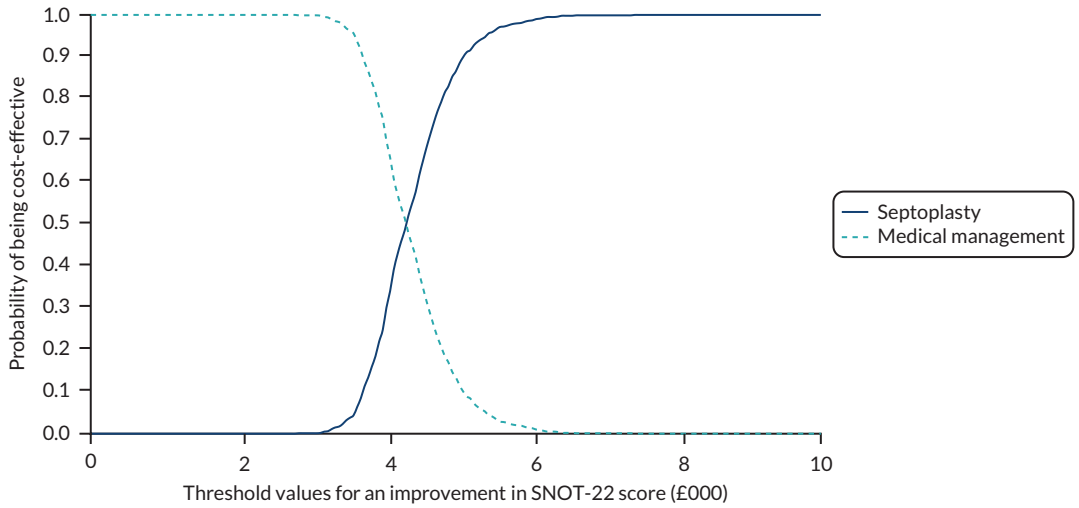

FIGURE 39 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CEA sensitivity analysis (costs and SNOT-22 score estimated at 6 months).

TABLE 79 Cost-effectiveness acceptability sensitivity analysis: AEs as the measure of effectiveness and costs estimated using multiple imputation

Investigation strategy	Cost (95% CI)[a] (£)	Incremental cost (95% CI)[b] (£)	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay to avoid an AE				
						£0	£500	£1000	£3000	£5000
Outcome: AEs – results										
Medical management (costs, *n* = 155; outcomes, *n* = 155)	973 (810 to 1137)	1193 (1018 to 1368)	0.542 (0.40 to 0.69)	0.302 (0.03 to 0.58)	Septoplasty is dominated	1.00	1.00	1.00	1.00	1.00
Septoplasty (costs, *n* = 152; outcomes, *n* = 152)	2162 (2102 to 2222)		0.836 (0.59 to 1.08)			0.00	0.00	0.00	0.00	0.00

a Point estimates are based on the unadjusted analysis (costs, *n* = 282; effects, *n* = 307).
b Incremental estimates are based on the adjusted analysis (*n* = 299).

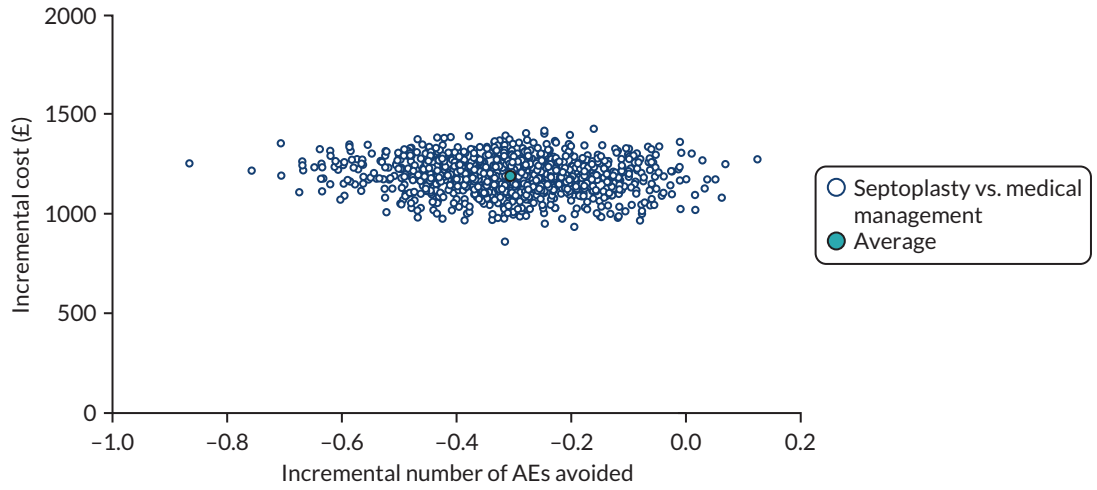

FIGURE 40 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CEA sensitivity analysis multiple imputation results (AEs as the measure of effectiveness).

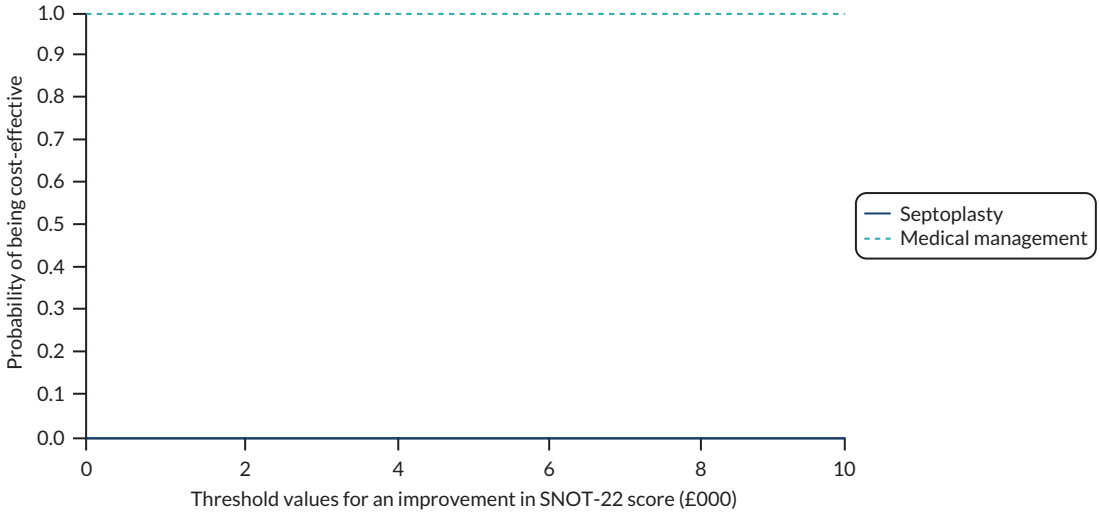

FIGURE 41 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CEA sensitivity analysis multiple imputation results (AEs as the measure of effectiveness).

TABLE 80 Cost–utility analysis sensitivity analysis: septoplasty costs estimated using microcosting

Investigation strategy	Cost (95% CI)[a] (£)	Incremental cost (95% CI)[b] (£)	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an additional QALY				
						£0	£10,000	£20,000	£30,000	£50,000
Outcome: surgery costs estimated using microcosting – results										
Medical management (costs, *n* = 155; outcomes, *n* = 152)	797 (650 to 884)	734 (608 to 860)	0.728 (0.71 to 0.75)	0.044 (0.03 to 0.06)	16,682	1.00	0.99	0.21	0.01	0.00
Septoplasty (costs, *n* = 152; outcomes, *n* = 149)	1500 (1453 to 1547)		0.767 (0.75 to 0.79)			0.00	0.01	0.79	0.99	1.00

a Point estimates are based on the unadjusted analysis (costs, *n* = 307; effects, *n* = 301).
b Incremental estimates are based on the adjusted analysis (*n* = 299).

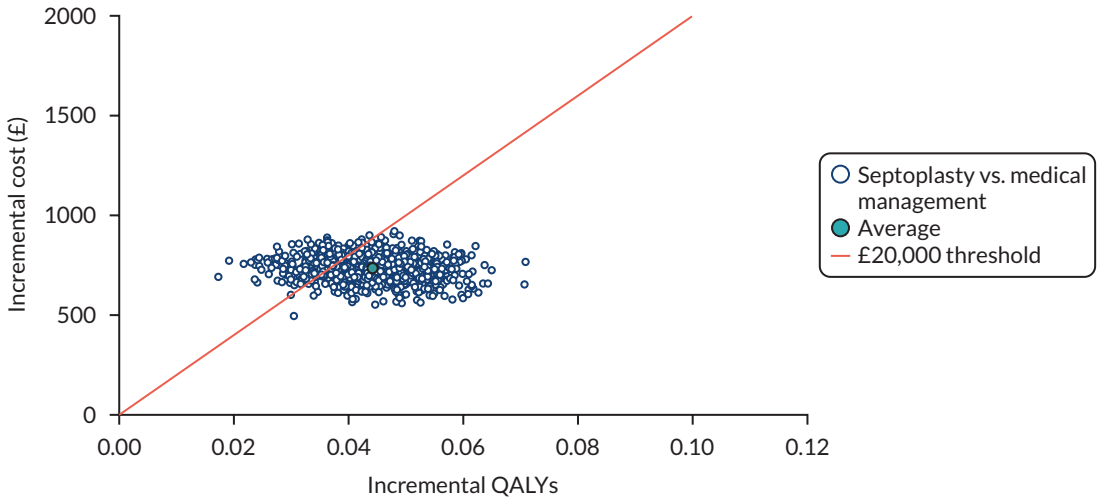

FIGURE 42 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis multiple imputation results (septoplasty costs estimated using microcosting).

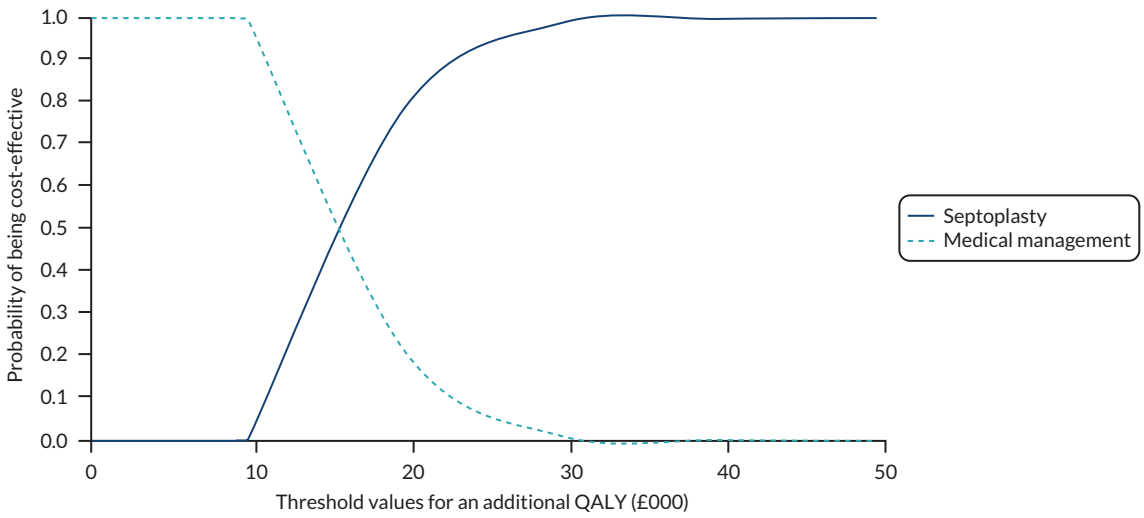

FIGURE 43 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis multiple imputation results (septoplasty costs estimated using microcosting).

TABLE 81 Cost–utility analysis sensitivity analysis: participant costs included in total costs

Investigation strategy	Cost (95% CI)[a] (£)	Incremental cost (95% CI)[b] (£)	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an additional QALY				
						£0	£10,000	£20,000	£30,000	£50,000
Outcome: participant costs included – results										
Medical management (costs, *n* = 155; outcomes, *n* = 152)	2054 (1644 to 2465)	1062 (532 to 1593)	0.728 (0.71 to 0.75)	0.044 (0.03 to 0.06)	24,136	1.00	0.98	0.71	0.27	0.02
Septoplasty (costs, *n* = 152; outcomes, *n* = 149)	3087 (2753 to 3421)		0.767 (0.75 to 0.79)			0.00	0.02	0.29	0.73	0.98

a Point estimates are based on the unadjusted analysis (costs, *n* = 307; effects, *n* = 301).
b Incremental estimates are based on the adjusted analysis (*n* = 299).

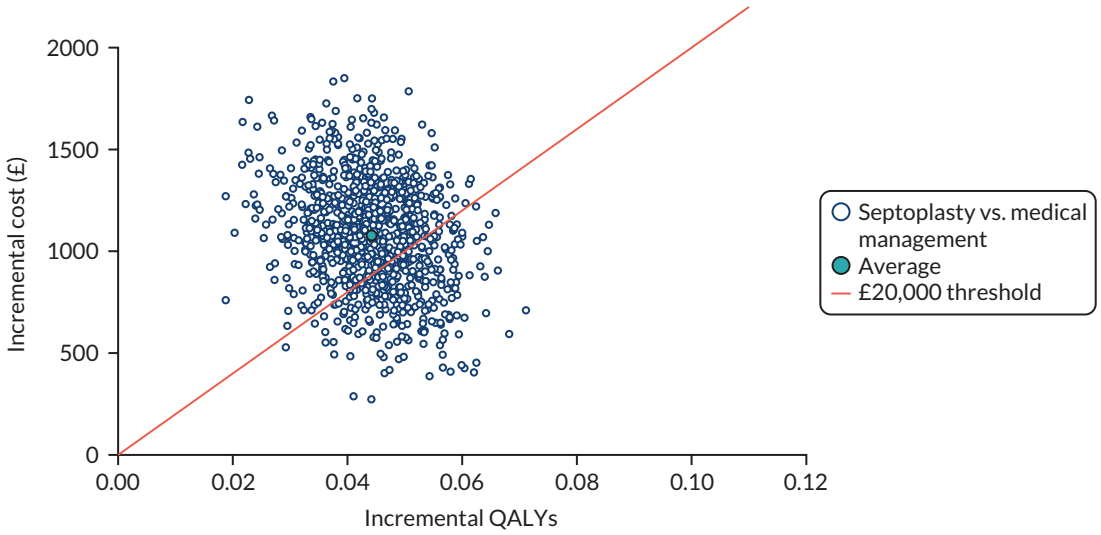

FIGURE 44 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis multiple imputation results (participant costs included in total costs).

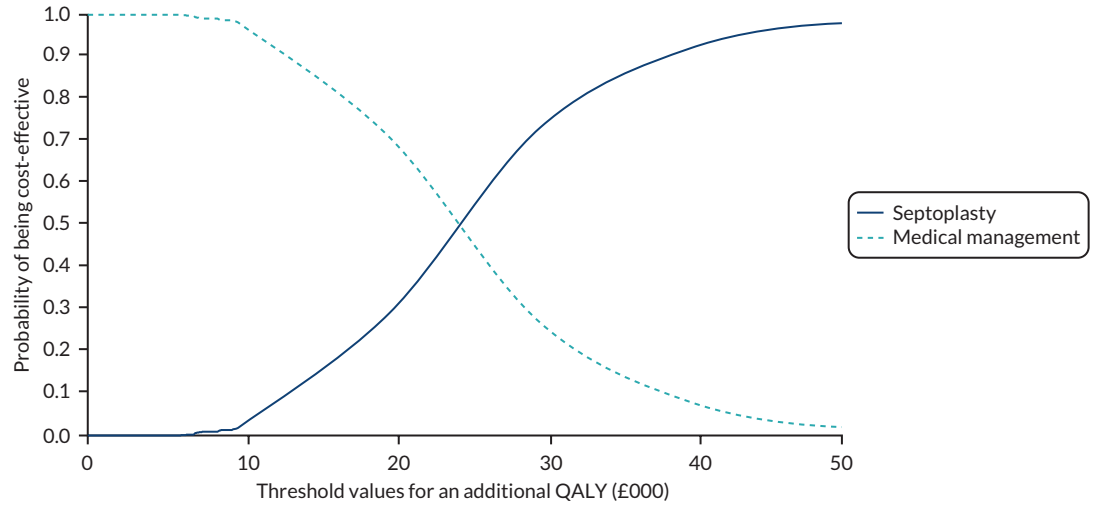

FIGURE 45 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis multiple imputation results (participant costs included in total costs).

TABLE 82 Cost–utility analysis sensitivity analysis: costs and QALYs estimated for those with complete data – no imputation

Investigation strategy	Cost (95% CI)[a] (£)	Incremental cost (95% CI)[b] (£)	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an additional QALY				
						£0	£10,000	£20,000	£30,000	£50,000
Outcome: complete case – results										
Medical management (costs, *n* = 109; outcomes, *n* = 111)	930 (744 to 1116)	1308 (1100 to 1515)	0.741 (0.72 to 0.76)	0.035 (0.02 to 0.05)	37,371	1.00	1.00	1.00	0.77	0.17
Septoplasty (costs, *n* = 95; outcomes, *n* = 99)	2207 (2134 to 2280)		0.761 (0.74 to 0.79)			0.00	0.00	0.00	0.23	0.83

a Point estimates are based on the unadjusted analysis (costs, *n* = 204; QALYs, *n* = 210).
b Incremental estimates are based on the adjusted analysis (*n* = 199).

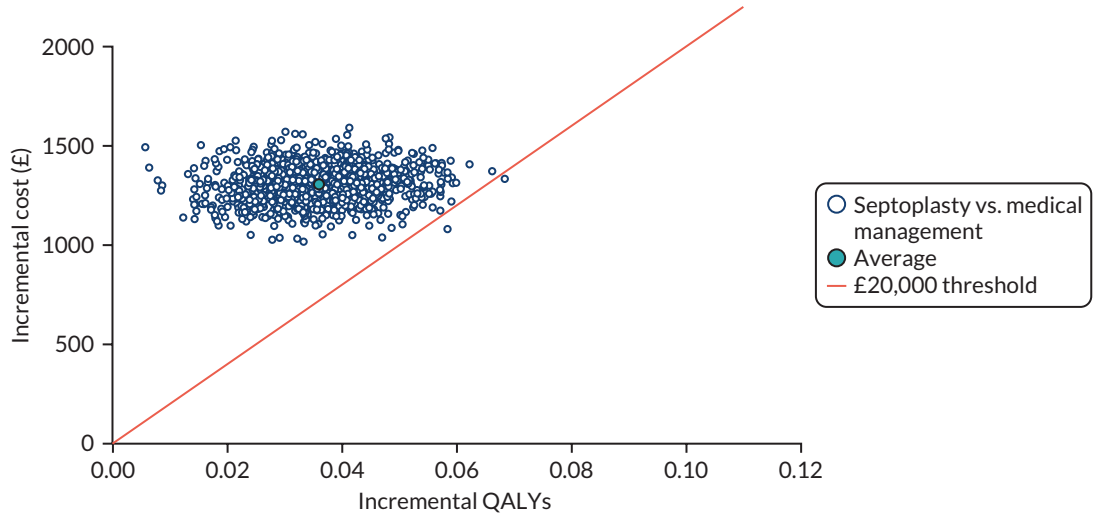

FIGURE 46 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis (costs and QALYs estimated for those with complete data – no imputation).

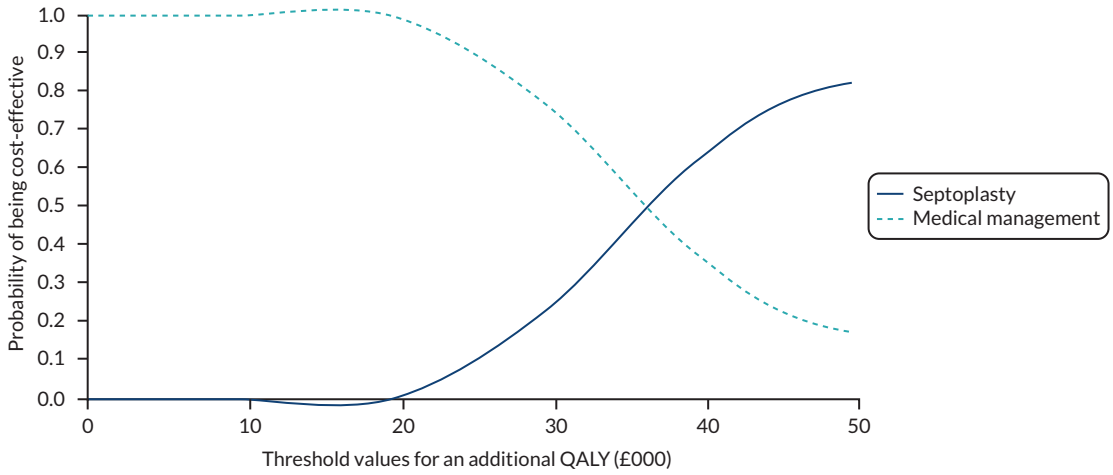

FIGURE 47 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis (costs and QALYs estimated for those with complete data – no imputation).

TABLE 83 Cost–utility analysis sensitivity analysis: changing eligibility criteria (NOSE category severe or extreme only)

Investigation strategy	Cost (95% CI)[a] (£)	Incremental cost (95% CI)[b] (£)	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an additional QALY				
						£0	£10,000	£20,000	£30,000	£50,000
Outcome: QALYs at 12 months – results										
Medical management (costs, *n* = 133; outcomes, *n* = 130)	1053 (872 to 1234)	1126 (936 to 1315)	0.715 (0.69 to 0.74)	0.049 (0.03 to 0.07)	22,980	1.00	1.00	0.76	0.11	0.00
Septoplasty (costs, *n* = 134; outcomes, *n* = 131)	2166 (2107 to 2225)		0.769 (0.75 to 0.79)			0.00	0.00	0.24	0.89	1.00

a Point estimates are based on the unadjusted analysis (costs, *n* = 267; QALYs, *n* = 261).
b Incremental estimates are based on the adjusted analysis (*n* = 259).

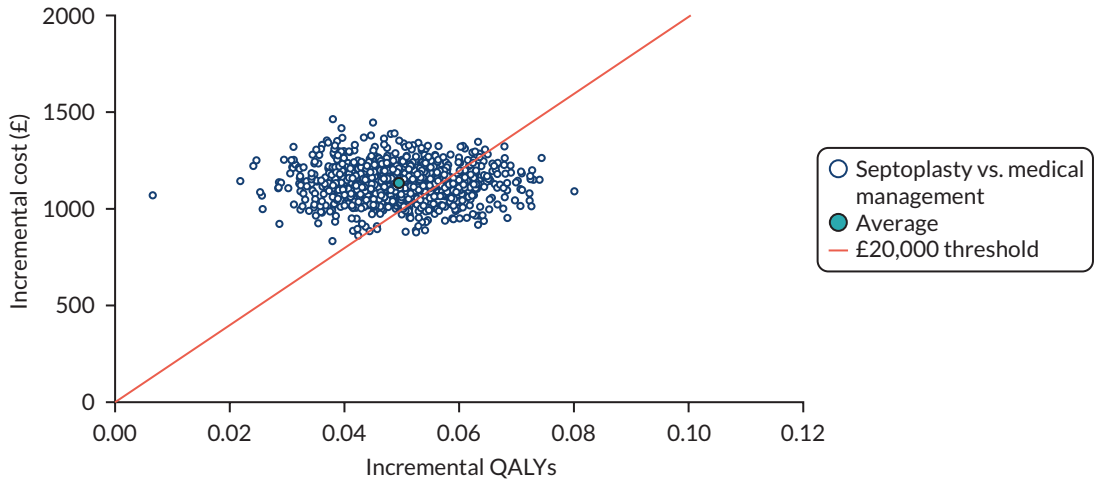

FIGURE 48 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis multiple imputation results (changing eligibility criteria).

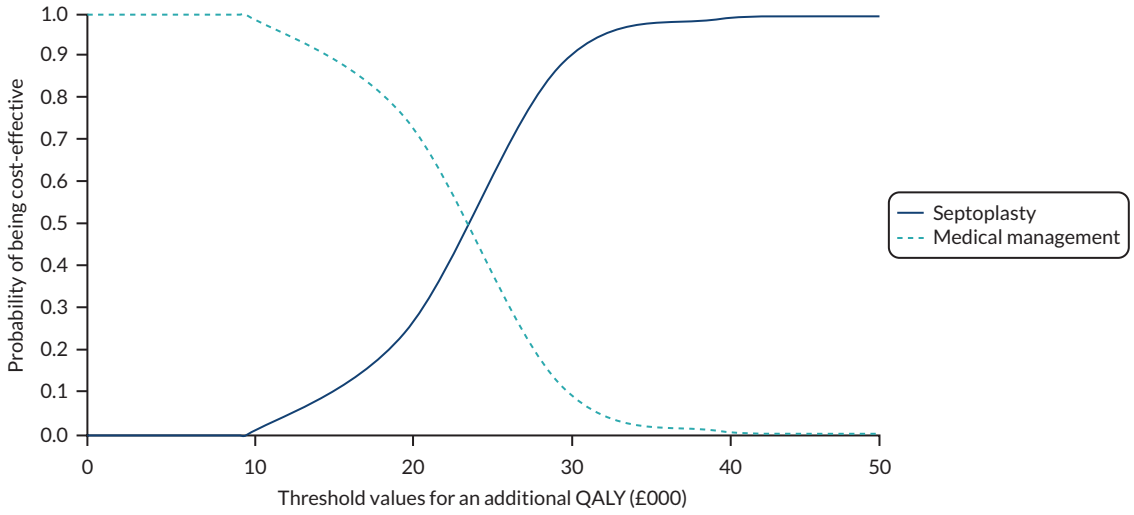

FIGURE 49 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis multiple imputation results (changing eligibility criteria).

TABLE 84 Cost–utility analysis sensitivity analysis: incremental cost per QALY at 6 months

Investigation strategy	Cost (95% CI)[a] (£)	Incremental cost (95% CI)[b] (£)	Effect (95% CI)[a]	Incremental effect (95% CI)[b]	ICER (£)	Probability that septoplasty is cost-effective for different threshold values for society's willingness to pay for an additional QALY				
						£0	£10,000	£20,000	£30,000	£50,000
Outcome: QALYs at 6 months – results										
Medical management (costs, *n* = 142; outcomes, *n* = 138)	294 (216 to 372)	1787 (1693 to 1881)	0.363 (0.35 to 0.37)	0.015 (0.01 to 0.02)	119133	1.00	1.00	1.00	1.00	1.00
Septoplasty (costs, *n* = 140; outcomes, *n* = 137)	2071 (2016 to 2125)		0.373 (0.36 to 0.39)			0.00	0.00	0.00	0.00	0.00

a Point estimates are based on the unadjusted analysis (costs, *n* = 282; QALYs, *n* = 275).
b Incremental estimates are based on the adjusted analysis (*n* = 269); missing cost and utility data were not imputed.

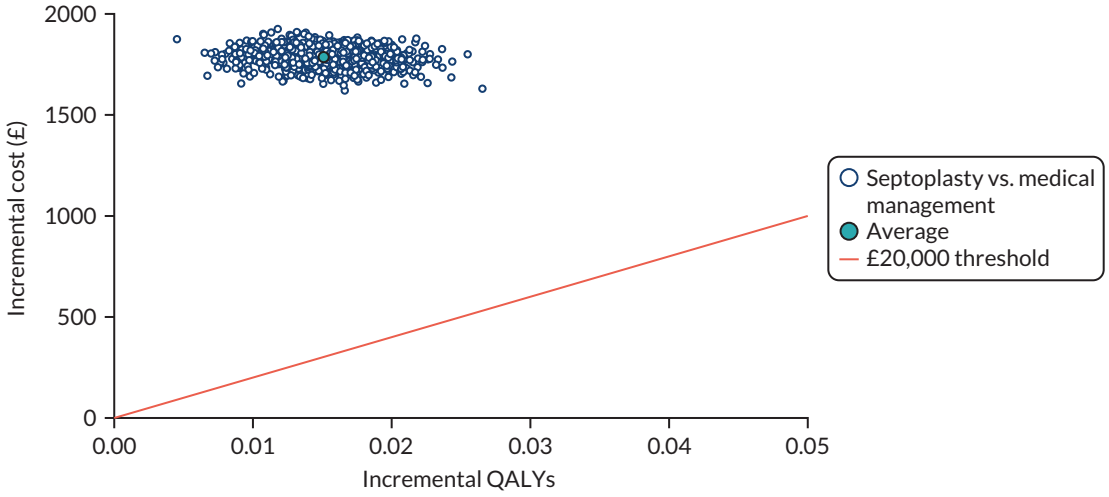

FIGURE 50 Cost-effectiveness plane for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis (incremental cost per QALY at 6 months).

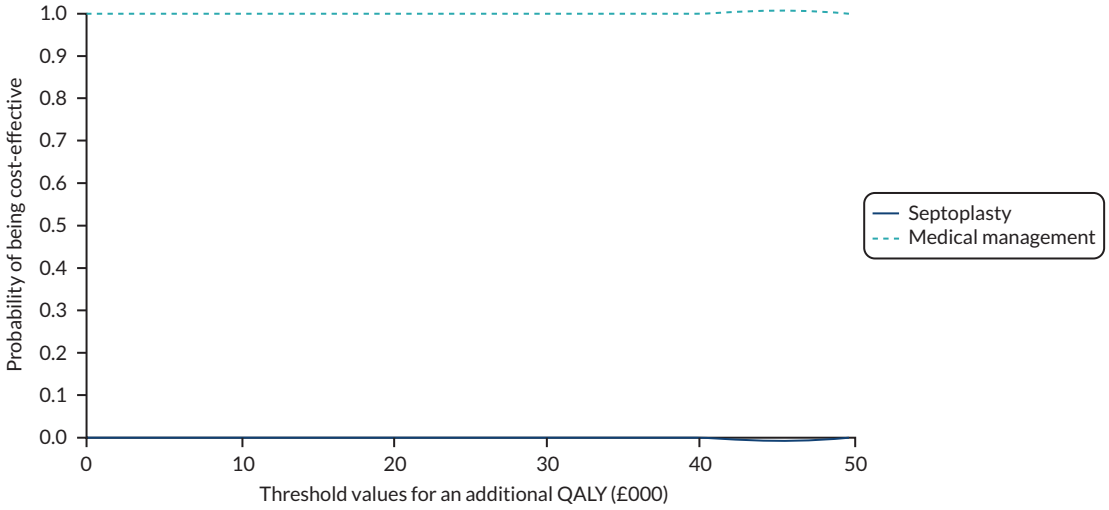

FIGURE 51 The CEAC for septoplasty vs. medical management using the adjusted bootstrapped CUA sensitivity analysis (incremental cost per QALY at 6 months).

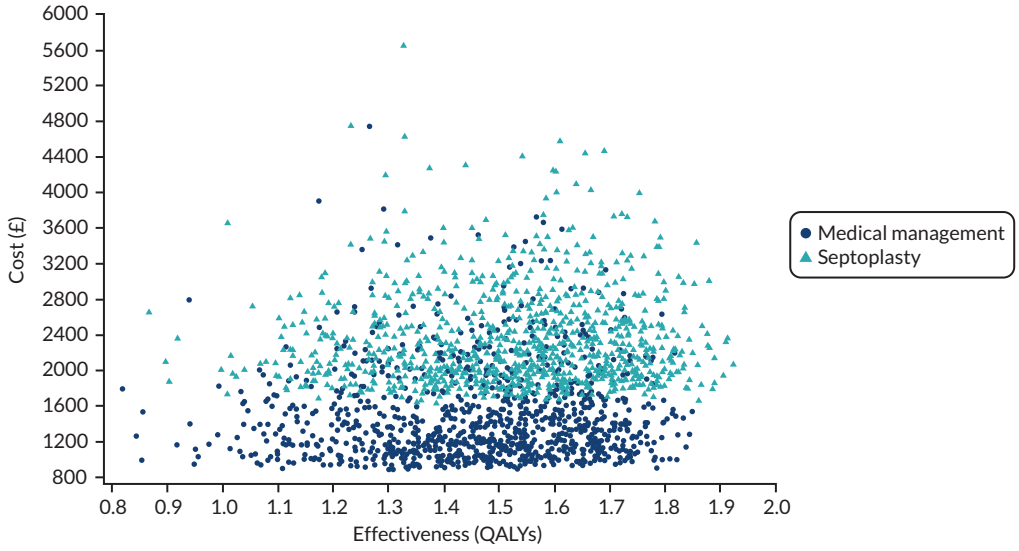

FIGURE 52 Cost-effectiveness plane for septoplasty vs. medical management based on the economic model (incremental cost per QALY at 24 months).

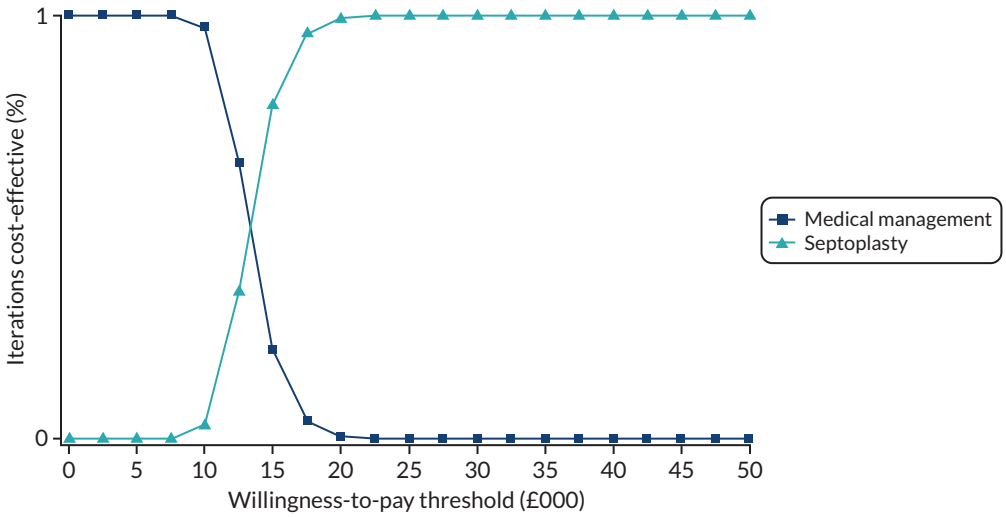

FIGURE 53 The CEAC for septoplasty vs. medical management based on the economic model (incremental cost per QALY at 24 months).

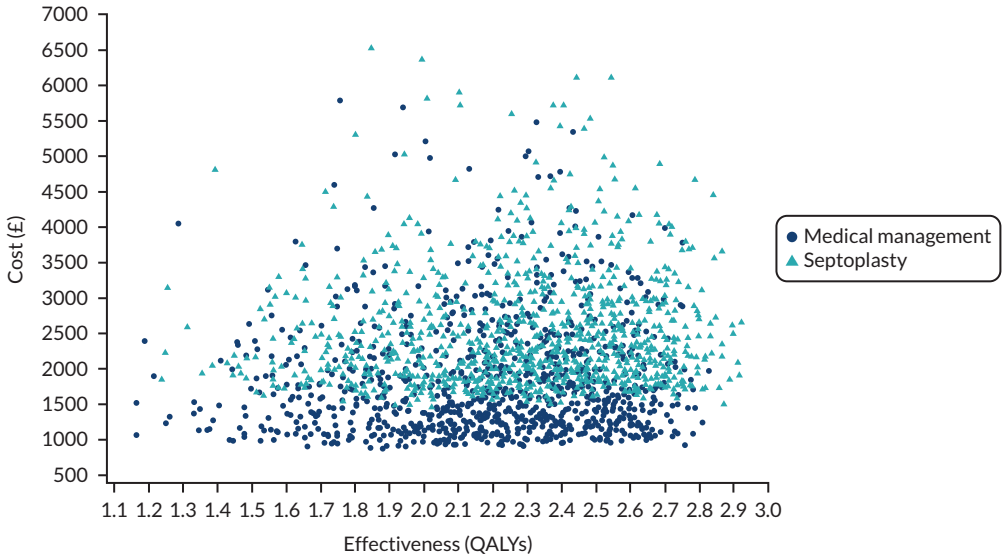

FIGURE 54 Cost-effectiveness plane for septoplasty vs. medical management based on the economic model (incremental cost per QALY at 36 months).

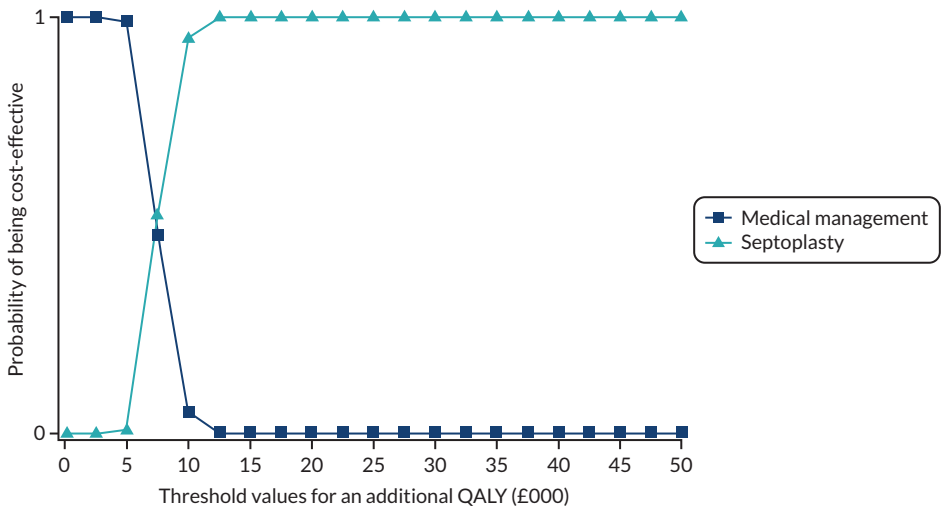

FIGURE 55 The CEAC for septoplasty vs. medical management based on the economic model (incremental cost per QALY at 36 months).

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