Short Title/Acronym: NASAL AIRWAY OBSTRUCTION STUDY

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

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Trial Website	http://www.nairos.co.uk

TRIAL SUMMARY

Trial Title	NAIROS - Nasal AIRway Obstruction Study

Acronym	NAIROS
Clinical Phase	Phase III
Summary of Trial Design	An open-label mixed methods trial, informed by an already executed feasibility phase, incorporating: Accelerated Start-up Internal Pilot with integrated QuinteT Recruitment Intervention to optimise recruitment; multicentre randomised controlled trial with qualitative process and economic evaluation, randomising participants on a 1:1 basis between immediate septoplasty versus medical management of nasal obstruction. Randomisation will be stratified by gender and severity (NOSE score moderate, severe, extreme).
Summary of Participant Population	Adults referred to secondary care with reduced nasal airway and a deviated nasal septum visible at nasendoscopy, baseline NOSE score ≥30, capacity to provide informed written consent and complete the trial questionnaires.
Inclusion Criteria	• Adults aged ≥ 18 years • Baseline NOSE score ≥30 • Septal Deflection at baseline visible via nasoendoscopy • Capacity to provide informed written consent and complete the trial questionnaires • Participants are willing and able to provide full written informed consent
Exclusion Criteria	• Any prior septal surgery • Systemic inflammatory disease or current oral steroid treatment • Granulomatosis with polyangiitis • Naso-endoscopic evidence of unrelated associated pathology e.g. adenoid pad, septal perforation, chronic rhinosinusitis indicated by the presence of polyposis or pus • Any current or prior? intranasal recreational drug use • Breast feeding, pregnancy or intended pregnancy for duration of involvement in the trial • Bleeding diathesis • Therapeutic anticoagulation (Warfarin/NOAC therapy) • Clinically significant contraindication to general anaesthesia

	• Patients known to be immuno-compromised
Planned Sample Size	378 (including estimated 20% drop-out)
Planned Number of Sites	10 sites for the pilot phase (With a contingency of up to 17 sites for the main trial)
Interventions	Septoplasty – Surgical intervention to straighten the nasal septum +/- contralateral turbinate reduction . Medical management – 6 months of using Sterimar (isotonic saline nasal spray) Class IIa device and Mometasone steroid nasal spray.
Formulation, Dose & Route of Administration	Mometasone = 100mcg (2 puffs in each nostril) to be taken twice daily for up to 6 weeks only. After 6 weeks 100mcg (2 puffs in each nostril) once daily or 1 puff in each nostril twice daily for the remainder of the 6 month period. Sterimar = 1 metred dose twice daily for each nostril for 6 months to be taken before Mometasone.
Follow Up Duration	12 months post randomisation
Planned Recruitment Period	20 months
Total Trial Duration	42 months
Primary Objectives	To establish, and inform guidance for, the best management strategy for participants with nasal obstruction associated with a deviated septum, via a randomised controlled trial: a. To compare the clinical and cost effectiveness over the complete period of 6 months, in adults with nasal septal deviation, the outcome of nasal septoplasty +/- contralateral turbinate reduction versus medical management. b. To apply ensuing NAIROS level I evidence to inform NHS guidance.
Primary Outcome Measures	SNOT-22 score at 6 months post randomisation

Secondary Objectives and Outcome Measures

Clinical effectiveness

a. Measure clinical effectiveness according to:
    i. Subjective self-report rating of nasal airway obstruction (NOSE, DOASS).
    ii. Heterogeneity of estimated treatment effect specifically according to severity of obstruction and gender.
    iii. Objective measures of nasal patency (peak nasal inspiratory flow rate and nasal partitioning ratio).
    iv. Quality-of-life as recorded by SF36.
    v. Safety profile recording the number of adverse events and additional interventions required.
b. To adjust the estimate of effectiveness in the light of other baseline covariates - severity of self-report nasal block (NOSE), gender and concomitant turbinate reduction.
c. To use the results in the surgical arm to explore a possible definition of technical failure in experienced hands .i.e. experienced surgeons, either consultants or non-consultant career clinicians, but not trainee otolaryngologists.
d. To 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 :

a. Cost-effectiveness measured in terms of the incremental cost per adverse event avoided and change in SNOT-22 score over 12 months. Cost-utility analysis reported as incremental cost per QALY gained (derived from SF- 36 and converted into SF-6D scores) over 12 months. A longer-term economic model to access costs and health consequences beyond 12-month follow-up period. All analyses will be conducted from the perspective of the NHS and participants.

Mixed Method Process Evaluation:

a. To understand the recruitment process in NAIROS through integration of the QuinteT Recruitment Intervention, with a view to identifying recruitment challenges, and devising a 'plan of action' to address these in collaboration with the trial management group (TMG).
b. To document the views and experiences of participants and clinicians regarding nasal septal surgery and medical management; further refine interventions and trial processes, assess willingness to randomise, and be randomised -including evaluation of patient expectation.
c. Assess implementation of trial findings – including some interviews with purposive sample of GPs who have had participants referred back to primary care with non-surgical intervention.

CE Medical devices

Nasal Patency is measured by two devices

1. Peak Nasal Inspiratory Flow (PNIF) Meter
2. NV1 Rhinospirometer

Route of Administration

The PNIF meter is a non-invasive device that assesses the maximum flow rate at which air flows through the nose (peak nasal inspiratory flow rate). The patient holds a mask over their nose and mouth and inhales maximally (sniffs) through their nose.

The NV1 Rhinospirometer is a non-invasive device that measures volumes of air passing through each nostril separately, for calculation of the nasal partitioning ratio (NPR). The patient breathes into two nosepieces connected to tubes attached to the device.

Further details on Interventions: Septoplasty

Septoplasty with or without reduction of the contralateral inferior turbinate. Returning the deviated septum to the midline and addressing an enlarged inferior turbinate corrects the anatomical cause of nasal obstruction.

Further details on Interventions: Medical management

A combination of nasal steroid spray and saline nasal spray. Feasibility work for the trial indicated that most referred participants had never had a combination of these treatment options. The standardised medical treatment arm offers an option that most participants will not have used previously and is in line with current treatment pathways. The investigator should ensure the patient understands that the saline

	spray should be taken before the Mometasone spray. The investigator should also ensure that the patient understands how to appropriately deliver the sprays into the nostril.
CE Medical device	Sterimar (isotonic saline nasal spray) Class IIa
Investigational Medicinal Product(s)	Mometasone

Contents

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
Bd	Twice a day
CA	Competent Authority
CBA	Cost–benefit analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CUA	Cost Utility Analysis
DMC	Data Monitoring Committee
DOASS	Double Ordinal Airway Subjective Scale (DOASS)
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
EMA	European Medicines Agency
ENT	Ear Nose and Throat
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HTA	Health Technology Assessment

IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
Mcg	Microgram
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NIHR	National Institute for Health Research
NIMP	Non-Investigational Medicinal Product
NPR	Nasal Partitioning Ratio
PI	Principal Investigator
PIS	Participant Information Sheet
PK	Pharmacokinetic
PNIF	Peak Nasal Inspiratory flow (rate)
PPI	Public and Patient Involvement
QA	Quality Assurance
QALY	Quality Adjusted Life year (quality of life assessment)
QC	Quality Control
QRI	Quintet Recruitment Intervention
R&D	Research & Development

RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SF-36	36-Item Short Form Health Survey
SF-6D	Health Economy Survey derived from SF-36
SIV	Site Initiation Visit
SmPC	Summary of Product Characteristics
SNOT	Sino-Nasal Outcome Test
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
USM	Urgent Safety Measure

1. BACKGROUND

Septoplasty is surgery to straighten the part of the nose that divides the two nostrils (the septum).

About 20000 septoplasty operations are carried out in the NHS each year. Ideally, the septum runs down the centre of the nose [1]. If it is not straight, perhaps because of injury, it may narrow one side of the nose and obstruct airflow. On the sidewalls of the nose are “turbinates”, tissue structures which are full of blood vessels and glands. Often when the septum narrows one side of the nose, it creates a larger space on the other side, into which the turbinate on that side expands. When surgery to straighten the septum is carried out, some surgeons also reduce the turbinate tissue.

Septoplasty is carried out in the hope of improving symptoms such as a blocked nose, snoring and sleep disturbance. Like any operation, there is a risk of complications. Most patients need to take at least 5 days off work or usual activities after the operation. Some patients seem not much better after the surgery. Practice varies around the country, and there is no good evidence about this operation or its alternatives, or about who might benefit most from treatment, to help patients and doctors decide when it should be carried out.

NAIROS aims to provide this evidence by randomising patients ≥ 18 years of age to either septoplasty or medical care (medical management). The medical management is a 6 months’ course of two nasal sprays – neither of which the patient is likely to have used before in a sustained manner. Surgeons in up to 17 NAIROS centres will continue to vary in their turbinate surgery, according to how they see individual patient needs. Operations involving any other procedure are excluded. Patients fill in symptom scores, quality of life scores and have nasal patency measures carried out at the time of randomisation, then at 6 and 12 months thereafter. This trial plans to look at the changes after surgery and medical treatment according to how bad their symptoms were in the first place, and if they are men or women. This will allow us, at the end of the trial, to recommend which patients groups, if any, stand to gain most from a septoplasty operation. Patients we consulted told us they would prefer to be randomised to “deferred” rather than “never” surgery so patients will be seen at 6 months to measure the primary outcome (22 item nasal symptom score) and given face to face feedback about their care, and enable a repeated measurement of nasal patency.

Our health economic analysis will look at the NHS costs of nasal blockage and also look at money spent by patients buying over the counter medicines, and the cost incurred by the time off work. We shall look at the frequency of complications. Randomising patients between surgical and medical arms can be difficult, we will assess recruitment and retention in an internal pilot phase and integrate the QuinteT Recruitment Intervention to identify and address recruitment challenges that can be mitigated [2]. This will include:

a. Mapping out patient pathways across sites and scrutinising screening log data
b. Audio-recording (with consent) discussions where health care professionals try to recruit eligible patients
c. Interviews with staff involved in trial oversight and trial conduct

Alongside the trial we will carry out interviews with patients and clinical staff. These interviews will help us to understand:

a. Why patients do or do not wish to take part in the trial?
b. Patients' experiences of septoplasty and the medical arm
c. How to put the findings of the trial into practice.

Nasal Obstruction Septoplasty Effectiveness (NOSE)

The NOSE scale is now a popular assessment of the outcomes of nasal obstruction surgery. The standard NOSE 5 items are scored 0 to 4, i.e. total score = 20. Conventionally the score is multiplied by 5, such that the maximum possible is converted to 100. The merits of NOSE are also its limitations - brevity and focus on nasal obstruction symptoms. A recent systematic review [3] of post-operative NOSE data on 643 patients undergoing a variety of surgical procedures showed an overall weighted mean change of 42/100 scaled points. Our departmental audit of a smaller but more relevant population – septoplasty and inferior turbinate reduction – gave broadly consistent results, mean reduction = 55 at 3 months [4].

Additional studies also had comparable NOSE scale change following septal surgery [5-9]. Lipan and Most [10] performed a receiver operating characteristic (ROC) analysis of NOSE scores obtained in a heterogeneous population of 345 patients undergoing nasal surgery. They defined a NOSE score less than 30 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 NAIROS, we predict, that as with most interventions, baseline severity will be the most important determinant of outcome – i.e. the effect we demonstrate will depend on the severity of disease in the sample studied. Those with NOSE score 30 or less are considered too mildly affected for NAIROS inclusion.

Double Ordinal Airway Subjective Scale (DOASS)

NAIROS uses this simple subjective comparator of right and left nasal patency alongside objective measurements of nasal patency. Patients are asked to gently seal one nostril with a finger before scoring.

This additional patient self-report tool was developed almost a decade ago by the Eccles group, to reflect patient awareness of this partitioning of airflow. Subjective scores, and investigator's assessment of septal deviation, were compared with the objective measurements of nasal partitioning ratio (NPR) in 46 patients waiting for septal surgery. Interestingly, about 20% of those listed for septal surgery had relatively symmetrical measured nasal airflow. Use of the then novel subjective ordinal scale to measure partitioning of airflow greatly increased the specificity of patient selection (correlation with NPR r=0.8) [11].

Sleep

The impact on sleep breathing disorders was key to many patients and GPs accessed in the NAIROS preparatory phase. We shall use the SNOT22 questionnaire to assess sleep impact. While nasal surgery also is not an effective treatment for obstructive sleep apnoea (OSA) as such [12] small septoplasty studies benefit in difficulty in falling asleep, waking at night [13] Or even snoring. [14] However, most reports are less optimistic [15], and the impact of septal surgery on snoring and sleep breathing disturbance is as unpredictable. The mode of action of septoplasty in sleep related breathing disorders may not be fully understood. A study showing improvements in sleep symptoms post septoplasty failed to show correlation with the degree of septal deviation (albeit perhaps not powered to do so.) [16]

Measurements of Nasal patency

Two different measurements of nasal patency will be conducted in this trial: peak nasal inspiratory flow rate (PNIF), made using the PNIF meter, and nasal partitioning ratio (NPR), made using the NV1 Rhinospirometer.

PNIF measures the peak flow rate of air through both nostrils during inhalation. The patient is asked to hold the mask over their nose and mouth and inhale maximally (sniff) with their mouth closed. PNIF has been shown to respond to septoplasty/turbinectomy and can therefore be used for an overall assessment of nasal airflow impairment, and as an objective outcome measure from surgery.

NPR is a standard pre-septoplasty assessment in many European countries. Bench testing shows the NV1 Rhinospirometer to be an accurate and precise objective marker of airflow symmetry [17]. NPR derived ranges from 0.00 (equality of airflow) to 1.00 (total unilateral obstruction). The normal range is defined as 0.00-0.34. NPR has a high correlation of 0.85 with observer assessment of the degree of deflection, and high correlation of 0.94 with patient subjective symptom assessment preoperatively, albeit only 0.51 postoperatively in one series [18]. The potential value of NPR in patient selection for septal surgery was further demonstrated in another cohort of patients, subjectively improved after septoplasty, yet of whom only those with baseline NPR abnormality had a significant postoperative reduction of NPR [19].

NAIROS proposes to make measurements of nasal patency measures at randomisation, 6 and 12 months thereafter . We propose to use the analogous patient report Double Ordinal Airway Subjective Scale for patient comparison of right and left nasal airway alongside each set of objective measurements.

Summary of Mometasone

Mometasone is a fluorinated nasal steroid spray for patients presenting with nasal obstruction in primary care, although it is not a first line of nasal steroid spray used by GPs. During NAIROS, patients randomised to the medical management arm will be asked to use the fluorinated steroid spray in combination with saline spray twice daily for 6 months as a standard medical management. It has become apparent that most patients referred from their GP have never had a combination of saline rinse with a full twice daily dose of a fluorinated steroid spray which is a typical maximal medical therapy regime. It has also become apparent that most GPs are no longer at liberty to prescribe this type of nasal spray due to their local prescribing restrictions.

Our aim is to standardise the medical management and to offer an option that most patients have not hitherto used and is in line with current pathways

Mechanism of action

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active. It is likely that the anti-inflammatory properties of Mometasone furoate are due to inhibition of a range of inflammatory mediators, such as inhibition of synthesis and release of IL-1, IL-6 and TNFα; it is also a potent inhibitor of leukotriene production. In addition, it is an extremely potent inhibitor of the production of the Th2 cytokines, IL-4 and IL-5, from human CD4+ T-cells [20].

2. RATIONALE

The NHS currently purchases thousands of surgical interventions on the nasal septum across the UK annually, yet the procedure is almost entirely lacking in a suitable evidence base, thus inevitably there are no well-defined selection criteria, particularly in patients whose principal symptoms are sleep related. The mode of action of septoplasty in sleep related breathing disorders may not be fully understood. A study showing improvements in sleep symptoms post septoplasty failed to show correlation with the degree of septal deviation (albeit perhaps not powered so to do.) The NHS and personal costs of this practice are considerable and urgently need evaluation in a substantive study with sufficient sample size and power to have real potential to influence clinical practice an, patient choice and NHS commissioning.

Currently, the vast majority of over 20 thousand UK annual septal operations are based entirely on subjective, unstandardized clinical impressions of the contribution of the nasal septum to patients' symptoms. The primary NAIROS output is a large scale account of the clinical effectiveness of septoplasty in adults with a deviated nasal septum. This will be a key piece of new knowledge, as currently such evidence is lacking world-wide. There will also be indicative costs applied to surgical and medical pathways. Surprisingly, objective assessment is the exception rather than the rule in the UK.

NAIROS includes objectives to record and assess baseline clinical factors to evaluate which may be potential determinants of outcome, and to estimate heterogeneity in any treatment benefit across these patient groups. The inclusion of a pragmatic, yet sensitive and specific objective baseline 'prediction' score might prove a key factor in determining the impact of NAIROS on current established practice and may characterise the variation in nasal dimensions a) pre and post decongestion; b) pre/ post-surgery.

The trial represents good value for money, since about £18 million of NHS money is spent on septoplasty operations each year, despite the fact that no one really know what the benefits are given there are no good quality randomised controlled trials.

2.1. Intervention – Septoplasty – Why septoplasty may not be the best option

Advantages of Septoplasty

- High levels of patient satisfaction
- One-off treatment which does not require lengthy medical therapy
- Level 3 evidence of efficacy

Disadvantages of Septoplasty

- Not standardised/no guidance on when to do it
- Variation across the country in numbers done
- No data on cost efficacy
- Risks associated with surgery
- Side-effects include rare but debilitating events such as septal perforation (expensive and at times impossible to correct)
- The economic cost of undergoing septoplasty – time off work, typically slow recovery period over several weeks

2.2. Intervention– Medical Management

Advantages of Medical Management

- No general anaesthetic required/no risks associated with surgery
- Low risk treatment/safe
- Standard treatment for nasal obstruction deliverable in primary care

Disadvantages of Medical Management

- Ongoing costs
- Patient could be undergoing indefinite medical therapy
- Potential for side-effects e.g. bleeding or nasal crusting
- May not be effective

Why choose Mometasone for the medical management arm?

Mometasone has the least amount of bio-availability compared to the other standard steroid sprays used according to the British National Formulary based on maximum benefit. Mometasone is the most effective, safest steroid spray and is untried adequately by the majority of likely participants based on previous work [21].

Medical therapy arm

Our feasibility work with ENT surgeons, GPs and newly referred nasal obstruction patients confirmed that most referred patients have never had a combination of saline rinse with a full twice daily dose of a fluorinated steroid (a typical maximum medical therapy regime). Indeed, certain GPs are no longer at liberty to prescribe this category of nasal spray due to local prescribing restrictions.

To both standardise the medical management and to offer an option a) that most patients have not hitherto used and b) is in line with current pathways, NAIROS participants in the medical management arm will be issued with a 6 months' supply of 'Sterimar' isotonic saline nasal spray (1 metred dose twice daily for each nostril) and 6 month's supply of Mometasone steroid spray, to be taken twice daily at 100mcg (2 puffs in each nostril) for up to 6 weeks. After 6 weeks 100mcg (2 puffs in each nostril) will be taken once daily or 1 puff in each nostril twice daily. Sterimar nasal spray is to be taken before the Mometasone steroid spray.

NAIROS compares septoplasty to medical management to determine the best nasal airway management strategy for patients with a deviated septum. NAIROS will map clinical and economic outcomes against best available potential outcome predictors to generate NHS evidence-based guidance on the spectrum of observed septoplasty benefit.

2.3. Risk Assessment

2.3.1. Septoplasty

Turbinate reduction may (depending on clinician assessment of individual patient need) be performed on the concave side at the time of septoplasty. This will minimise risks of postoperative intranasal adhesion and of causing a contralateral blockage postoperatively. The method of turbinate reduction will be by one of several available submucosal approaches and

largely focus on the anterior segment (which has greater impact on nasal patency). Any variance from the intention to reduce or not reduce the concave side turbinate will be recorded in as part of the operative detail in the NAIROS database.

The disadvantages of Septoplasty are:

The immediate surgical risks of septoplasty are discomfort in the nose, congestion and minor ooze of blood from nostrils. The rare side effects of septoplasty are heavier bleeding requiring a nasal pack and stay in hospital, numbness of upper teeth, scarring inside nose, decreased sense of smell, perforation (hole forms in septum which can cause whistling noise in breathing through nose) minor change in nose shape and a need for revision operation.

In general the expected side effects of general anaesthesia are transient drowsiness, shivering, dizziness and nausea. The rare side effects of general anaesthesia can include a minor sore throat which usually settles within a day or two with paracetamol (2 in 5 patients).

The advantages of Septoplasty are:

- High levels of patient satisfaction
- One-off treatment which does not require lengthy medical therapy
- Level 3 evidence of efficacy

2.3.2. Medical management

The disadvantages of Medical Management are:

- Ongoing costs
- Patient could be undergoing indefinite medical therapy
- There is a potential for side effects e.g. bleeding or nasal crusting
- May not be effective

The advantages of Medical Management are:

- Mometasone has a marketing authorisation in the UK and will be dispensed and managed as per non-trial medication by the hospital pharmacy department.

- Mometasone is licensed in dosage and form for use in patients with reduced nasal airway and a deviated nasal septum in the UK and is standard care for this indication.
- No general anaesthetic is required and there are no risks associated with surgery.
- It is a low risk treatment.

Therefore, from an investigational medicinal management (IMP) perspective, the risk to trial participants, related to the use of this drug in the trial, is comparable to the risk during standard care of nasal conditions.

2.3.3. Other risks

Apart from the above interventions, questionnaires and qualitative component of the trial, participants in both arms of the trial will be subject to routine clinical care only and we therefore consider that the risk associated with trial participation other than those related to the IMP and septoplasty are also low.

Risks associated with the design and methods of the trial including the clinical procedures specified in the protocol, patients' rights related to consent and protection of data and the reliability of trial results have also been assessed. The robust design of the trial to mitigate and manage these risks has led to the decision to submit this trial as a 'Type A' status (low risk - notification only) to the MHRA and allow for a risk-proportionate trial management and monitoring approach to the trial. A structured Safety Monitoring Plan will be constructed to assess risk management by all relevant parties including the sponsor, regulators, pharmacists, and regulatory and governance staff. This will be submitted to the MHRA along with the notification application.

The devices used to make measurements of nasal patency (PNIF meter and NV1 Rhinospirometer) are non-invasive and extremely low risk, simply requiring the patient to breathe into a mask or nosepieces.

2.3.4. Risk Category

This trial is categorised as:

- Type A = no higher than the risk of standard clinical care

3. OBJECTIVES AND OUTCOME MEASURES

The main aim is to establish, and inform guidance for, the best management strategy for patients with nasal obstruction associated with a deviated septum via a randomised controlled trial comparing immediate versus delayed surgery.

3.1. Primary Objective

- To compare clinical and cost effectiveness over a complete duration of 6 months in adults with a nasal septal deviation who have been referred to otolaryngology outpatient clinics with nasal airway obstruction, randomised between nasal septoplasty +/- contralateral turbinate reduction and medical management
- To apply the NAIROS level I evidence to inform NHS guidance

3.2. Secondary Objectives

The secondary objectives are split into 3 different aspects: clinical effectiveness, economic evaluations and mixed method process evaluation.

Clinical Effectiveness:

- To measure clinical effectiveness according to:
    - Subjective self-report rating of nasal airway obstruction with objective clinical measures
    - 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 and additional interventions required
- To adjust the estimate of effectiveness in the light of other baseline covariates - severity of self-report nasal airway obstruction, gender and concomitant turbinate reduction
- To use the results in the surgical arm to explore a possible definition of technical failure in experienced hands .i.e. experienced surgeons, either consultants or non-consultant career clinicians, but not trainee otolaryngologists
- To 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 to compare:

- The cost-effectiveness measured in terms of the incremental cost of adverse event avoided and change in SNOT-22 score over 12 months.
- The cost-utility with outcomes reported as incremental cost per QALY gained (derived from SF- 36 and converted into SF-6D scores) over 12 months.
- A longer term economic model to assess costs and health consequences beyond 12 month follow-up period.
- All analyses will be conducted from the perspective of the NHS and participants.

Mixed Method Process Evaluation of the Trial and Interventions:

Our mixed method process evaluation will identify, describe, understand and address:

- Barriers to optimal recruitment, and potential solutions to address these, through integration of the QuinteT Recruitment Intervention
- Participants' and health care professionals' experiences of trial participation and the interventions under evaluation
- Factors likely to influence wider implementation of trial findings.

3.3. Outcome Measures

3.3.1. Primary Outcome Measure

SNOT-22 score at 6 months post randomisation

3.3.2. Secondary Endpoints/Outcomes

- Longer term measures: Subjective - SNOT-22 subscales (Rhinologic, Sleep, Ear/facial pain, Psychological) at 12 -months; NOSE scale at baseline, 6-months and 12-months
- Safety measures: Number and characteristics of any adverse events and surgical complication/ failure and re-intervention within 12-months
- SF-36, further converted into QALYs using SF-6D Algorithm 129 longitudinally at baseline, 6-months and 12-months
- Use of and timing of additional interventions in primary and secondary care recorded at 6-months and 12-months

- Number of days unable to undertake usual activities recorded by Health Care Utilisation Questionnaire, at 6 months and at 12 months.

Economic Outcomes include:

- Incremental cost per
    - Change in SNOT-22
    - QALY gained (based on responses to SF-36)
    - Adverse Event avoided
- Costs to NHS and participants at 12 months
- Longer term economic model to assess costs and health consequences beyond 12 month follow-up period

Qualitative outcomes as identified through:

- Observations of training and NAIROS meetings
- Interviews with health professionals and participants
- Audio-recording of recruitment discussions

3.3.3. Other Measures

3.3.3.1. QuinteT Recruitment Intervention (QRI)

The process evaluation incorporates the Quintet Recruitment Intervention (QRI) to optimize recruitment, and mixed qualitative methods to understand participants' and health care professionals' experiences of septoplasty and medical management. Data collection and analysis will commence during trial set up and continue throughout the trial. The QRI will coincide with the trial set-up and internal pilot phases, using qualitative and novel methods to investigate and address recruitment barriers (objective 'a'). Qualitative interviews and focus groups will be conducted throughout the trial to investigate participants' and clinicians' experiences of the trial procedures, interventions, and barriers to implementing findings into practice (objectives 'b' and 'c').

Objective a: Optimising recruitment - Quintet recruitment intervention (trial set up and internal pilot phases)

The QRI aims to optimise recruitment and informed consent during the internal pilot phase of NAIROS. The QRI uses novel qualitative and mixed-method approaches pioneered during the NIHR HTA-funded ProtecT (Prostate testing for cancer and Treatment) study [22]. These methods have since been applied to several other 'challenging' or controversial randomised controlled trials (RCTs) in different clinical contexts, all of which have led to insights about recruitment issues and the development of generic and bespoke strategies to optimise recruitment [2].

The QRI will proceed in two iterative phases: a detailed understanding of the recruitment process will be developed in phase I, leading to tailored interventions to improve recruitment in phase 2.

Phase 1

Phase I will focus on building up a comprehensive understanding of recruitment challenges that arise during the internal pilot recruitment period of NAIROS. A multi-faceted, flexible approach will be adopted, using one or more of the following methods:

a) Mapping patient eligibility and recruitment pathways:

Detailed eligibility and recruitment pathways will be compiled for clinical centres, noting the point at which participants receive information about the trial, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other centres to identify practices that are potentially more/less efficient. The qualitative researcher will also work closely with the clinical trials unit (CTU) to compose detailed logs of potential RCT participants as they proceed through screening and eligibility phases, to help identify points at which patients do not continue with recruitment to the RCT. Logs of eligible and recruited participants will be assembled using simple flow charts and counts to display numbers and percentages of participants at each stage of the eligibility and recruitment processes. These figures will be compared across centres, and considered in relation to estimates specified in the grant application/trial protocol.

b) Audio recording and observation of recruitment appointments:

Scheduled appointments during which the trial is discussed will be audio-recorded and/or observed with permission, including telephone conversations. All staff involved in consenting participants to the trial will be invited to audio-record their discussions with participants using an encrypted digital recorder. The audio recordings will be used to explore information provision,

recruitment techniques, and management of patient treatment preferences. These recording will be integral to providing supportive feedback and training for recruiters (see Phase 2). Recordings will be transferred to and from the University of Bristol (for analysis) through University of Bristol-approved secure data transfer facilities and/or encrypted flash drives that adhere to NHS Trust policies.

c) Semi-structured Interviews may be conducted with the following groups:

- Members of the TMG, including the chief investigator (CI) and those closely involved in the design, management, leadership and coordination of the trial (n=5-10)
- Clinical and recruitment staff across all centres delivering the RCT (n=10-15)
- Eligible participants who are approached to take part in the RCT (n=5-10)

Interviews with TMG members/recruiters will explore perspectives on the RCT and their experiences of recruitment (where relevant). Key topics explored will include perspectives on the trial design and protocol; views about the evidence on which the trial is based; perceptions of uncertainty/equipoise in relation to the RCT arms; views about how the arms/protocol are delivered in their clinical centre; methods for identifying eligible participants; views on eligibility, and examples of actual recruitment successes and difficulties.

Interviews with participants will explore views on the presentation of trial information, understandings of trial processes (e.g. randomisation), and reasons underlying decisions to accept or decline the trial. Participants will be purposefully sampled, to build a sample of maximum variation on the basis of age, gender, trial centre, and the final decision about trial participation (i.e. accept or decline). The precise numbers of informants interviewed for each group will be guided by the concept of data saturation and pragmatic considerations (e.g. timing, numbers of 'key informants'). The numbers specified in brackets are simply estimates, based on experiences from QRIs integrated into previous RCTs.

QRI interviews will take place at a mutually convenient location, in a suitably private and quiet setting. All participants will be offered the option to conduct the interview over the telephone.

d) Observation of TMG and investigator meetings:

The QuinteT researcher will observe and potentially audio-record these meetings, with permission. The aim will be to gather further information about specific issues that may have a bearing on recruitment. These meetings can also elucidate new solutions to recruitment difficulties.

e) Document analysis of trial materials:

The Patient Information Sheet for the main trial, trial protocol, and other trial literature will be scrutinised to identify aspects that are unclear or potentially open to misinterpretation, thus having a possible bearing on recruitment.

Phase 2: Development and implementation of recruitment strategies

Findings from Phase 1 will be presented to the CI and TMG (with permission from CI). If recruitment difficulties are evident across the trial or in particular centres, the TMG and QuinteT team will formulate a 'plan of action' to improve recruitment and information provision. The specific plan implemented will be grounded in the findings from phase 1, with its format dependent on the nature of the recruitment barriers identified. For instance, generic challenges such as how to explain trial processes (e.g. randomisation) may be addressed through dissemination of 'tips and guidance' documents. Supportive feedback will be a core component of the plan of action, with the timing and nature of feedback dependent on the issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from group discussion. All group feedback sessions will be aided by anonymised data extracts from interviews and audio-recorded appointments. Individual confidential feedback will also be offered – particularly where recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues. Investigator meetings and site visits may also be conducted to discuss technical or clinical challenges (e.g. discomfort surrounding eligibility criteria).

Iterative nature of Phases 1 and 2

The QRI has been presented as two distinct phases for clarity, although in reality these are likely to overlap or run in tandem. For instance, new avenues of enquiry may emerge through feedback meetings, which can be a route to investigating recruitment difficulties in their own right. Insights into recruitment can emerge at any point during the trial, and instigate further investigations (phase 1) or intervention (phase 2).

Evaluating changes in recruitment practice and randomisation

The impact of QRI interventions implemented in phase 2 will be evaluated through mixed approaches, including 'before/after' comparisons (number of recruited participants, eligible participants identified, participants accepting allocation), and investigation of changes in recruiters' practices (through continued analysis of audio-recorded appointments). Semi-structured interviews may be conducted with recruiting staff and TMG members to explore their views on QRI interventions and suggestions for areas that would benefit from continued QRI input.

Objectives B and C: Understanding experiences of septoplasty and medical management

We will investigate participants' (n=16-20) and health professionals' (n=16-20) experiences of the interventions and trial participation through qualitative interviews, conducted during patient follow up. Where possible, participants for the follow up interviews will include those interviewed during the recruitment phase; additional participants will be recruited based on purposive and emergent criteria (e.g. participants who have crossed over to the other intervention arm). We will identify any aspects of the care pathway which are problematic for participants or health professionals; and potential barriers and facilitators to wider acceptance and implementation of trial findings. A focus group of GPs (or individual interviews depending on availability) will explore preliminary trial findings and discuss implications for primary care management of nasal obstruction.

3.3.3.2. Quality of Life

The within trial analysis will also compare changes in health related quality of life, based on responses to the SF-36 which is most likely to be sensitive to changes in health related quality of life in this population. The SF-36 will be administered at baseline, 6 and 12 months. Responses to the SF-36 will be converted into SF-6D scores using standard algorithms [23] and used to estimate quality-adjusted life years (QALYs). Costs and outcomes beyond the trial period will be taken into consideration using a longer term economic model.

3.3.4. Exploratory Outcome Measure

The two most common objective measures of nasal patency, used in some overseas healthcare systems to assess likely benefit from septoplasty, are peak nasal inspiratory flow rate (PNIF) and

nasal partitioning ratio (NPR). The two standard measurements will be made at baseline, 6 and 12 months following randomisation. At all three visits, the measurements will be made both before and after decongestant. Full measurement instructions are given in the nasal patency measurements SOP.

PNIF measures the peak flow rate of air through both nostrils during inhalation using a PNIF meter with face mask (shown below). The patient is asked to hold the mask over their nose and mouth and inhale maximally (sniff) with their mouth closed. PNIF has been shown to respond to septoplasty/turbinectomy and can therefore be used for an overall assessment of nasal airflow impairment, and as an objective outcome measure from surgery.

The NV1 Rhinospirometer measures the volume of air passing through each nostril, allowing calculation of the nasal partitioning ratio (NPR). This is the difference between right and left volumes divided by the sum, ranging from symmetrical (0) to completely unilateral (±1). The NV1 Rhinospirometer (shown below) has two separate channels to measure flow through each nostril concurrently. Ostensibly, the NPR relates to the degree of septal deviation. Previous published clinical work has shown that NPR could predict the likely benefit of surgery for septal deviation. We will measure NPR during both maximal inhalation and normal tidal breathing in order to assess which measurement is more useful.

NPR and PNIF are complimentary, since PNIF relates to overall impairment of nasal airflow, whereas NPR measures an asymmetry in airflow. We will use these measurements to assess the outcome of surgery carried out during the trial. Both the PNIF meter and the NV1 Rhinospirometer are supplied by GM Instruments (Kilwinning, UK).

In addition to the NPR, the NV1 Rhinospirometer obtains a measurement of nasal flow rate versus time for each nostril. This information can be saved and exported from the NV1 Rhinospirometer software then analysed using standard mathematical software. We will explore the relationship between parameters from this novel information, along with the standard measures of PNIF and NPR), and outcome from treatment.

The Trust may make available an anonymised subset of the data from the trial to enable GM Instruments to test the implementation of the algorithms.

4. TRIAL DESIGN

4.1. Main Trial

This is an open-label mixed-methods multi-centre (up to 17 centres in England, Scotland and Wales) randomised controlled trial, informed by using an already executed feasibility phase, which incorporates an accelerated start up internal pilot with qualitative process and economic evaluation randomising participants on a 1:1 basis between immediate septoplasty versus medical management of nasal obstruction. Randomisation will be stratified by gender and severity (Nasal Obstruction Symptom Evaluation). The primary analysis is comparison of the comprehensive, validated SNOT-22 patient reported scores at 6-months from randomisation, with complete follow-up of participants to 12 months post randomisation.

4.2. Pilot study

NAIROS includes a 5 month pilot phase (10 sites) to precede the full RCT. The pilot will look at all aspects of feasibility, safety and efficiency for NAIROS to optimise recruitment, a mixed method process evaluation and an economic evaluation. A planned assessment of recruitment and compliance to the protocol will be reported to enable the DMC to make recommendations for continuation with the trial.

5. TRIAL SETTING

This trial will take place in up to 17 centres in England, Scotland and Wales. Patient Information sheets will be sent along with the appointment for the ENT clinic and the patient recruited on visit 1 if eligible. If patients are identified in a general ENT clinic, the option of joining the trial can be explained to them. If they wish to proceed, the PIS can be given at that point and they can then be referred to the NAIROS clinic.

Recruitment will take place over 20 months (5 month pilot phase, 15 month RCT) with trial completion at 42 months (submission of final report).

6. ELIGIBILITY CRITERIA

Eligibility must be assessed by a medically qualified doctor and this assessment documented in the participant's medical notes. Only personnel formally delegated by the Principal Investigator to assess eligibility on the trial-specific delegation log may perform this task.

6.1. Inclusion Criteria

- Adults aged ≥ 18 years
- Baseline NOSE score ≥30
- Septal Deflection at baseline visible via nasoendoscopy
- Capacity to provide informed written consent and to complete the trial questionnaires.
- Participants are willing and able to provide full written informed consent

6.2. Exclusion Criteria

- Any prior septal surgery
- Systemic inflammatory disease or current oral steroid treatment
- Granulomatosis with polyangiitis
- Naso-endoscopic evidence of unrelated associated pathology e.g. adenoid pad, septal perforation, chronic rhinosinusitis indicated by the of polyposis or pus
- Any intranasal recreational drug use
- Breast feeding, pregnancy or intended pregnancy for duration of involvement in the trial
- Bleeding diathesis

- Therapeutic anticoagulation (Warfarin/NOAC therapy)
- Clinically significant contraindication to general anaesthesia
- Patients known to be immuno-compromised

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS ARE NOT PERMITTED.

7. TRIAL PROCEDURES

7.1. Recruitment

7.1.1. Patient Identification

Primary care clinicians may refer adults with a suspected nasal septal deviation directly to a NAIROS clinic. Otherwise NAIROS eligible patients will be proactively identified by researchers from general ENT referrals where possible. This will be through triage of non-e book patients, and scrutiny of 'Choose and Book' referral letters of potentially eligible rhinology patients where the appointment can be at an earlier date in a NAIROS clinic. Patients attending a NAIROS clinic will, where possible, have been sent the Patient Information Sheet with their appointment details, and have been directed to the Patient Information video, uploaded to www.NAIROS.co.uk. This will allow, where appropriate, enrolment at Visit one. Patient identification requires the NAIROS team to assess nasal block patients for NAIROS eligibility.

7.1.2. Screening and referral process

Potential participants will be screened against the inclusion and exclusion criteria using the clinic lists and patient medical notes. Local GPs will also refer any eligible patients to the ENT clinic.

7.2. Consent

At the beginning of the trial discussion patients will be asked to consent to complete a few short questionnaires and nose examinations to determine if they are eligible for the study (section 1 of the Main consent form). In order to complete eligibility, written informed consent must be provided by the patient and this must be witnessed by a member of the research team who has documented and delegated responsibility so to do.

Once the clinician has determined that the patient is eligible for the study the patient will be asked for their verbal permission and written confirmation (section 2 of the Main consent form) to audio-record the discussion about the NAIROS study.

A delegated member of the research team (as per the delegation log) will undertake informed consent discussions with the opportunity for the patient to ask any questions and discuss the trial in more detail. All patients will have been given a minimum interval of 24 hours after receiving the Patient Information Sheet to decide whether or not they would like to take part. If the patient decides to take part in the main study they will be asked to consent to section 3 of the main consent form.

The original signed consent forms will be retained in the Investigator Site File (ISF), with a copy filed in the clinical notes, a copy provided to the patient and a copy faxed to NCTU.

7.3. Qualitative Sub-Study

Audio-recording recruitment discussions for the QRI: Patients will be sent a copy of the information pertaining to recording recruitment consultations in the post. Recruiters will check if the patient has any questions about the recording process at the first recruitment appointment, and then seek written consent to record the discussion. Patients who agree will sign a one-off consent form that seeks permission to record future discussions about the trial in the lead up to the patient making their decision about participation.

A two-step consent process will apply in scenarios where patients have not received the written information about the recording process or main RCT in advance. Patients will be asked to provide verbal consent for the recruiters to record the initial appointment, and will be provided with the relevant patient information sheets about the recording process and RCT. Patients who agree to their appointments being recorded/observed will provide written consent in their subsequent appointment with the recruiting clinician/nurse. Future discussions will be audio recorded subject to receiving this written consent; if patients do not consent to their appointments being audio-recorded, the recording of their initial appointment will be deleted, and no further recordings made.

All those present who gave written informed consent for the discussion to be audio-recorded will be given a follow up information sheet to explain how they can contact the research team or qualitative researcher should they change their mind about the recording.

7.3.1. Patient Interviews

During the trial consent discussion all patients (even those who do not wish to take part in the main trial) will be asked if they can be contacted about a telephone interview. Not all patients who consent to be contacted about an interview will be contacted. Patients who consent and are to be interviewed will be contacted a few weeks after the recruitment discussion, and around the date of their 6 month or 12 month visit. There will be no more than 2 interviews per patient.

Patients will be given an Interview Patient Information Sheet to take away with them for consideration and asked for written consent to be contacted, allowing their details to be passed securely to the research team. The qualitative researcher will telephone the patient and, if the patient agrees, arrange a convenient time and date to conduct the interview. Verbal consent will be obtained at the very start of the call, including to audio-record the interview. The recorder will be switched on and the researcher will go through the consent form questions before the interview starts.

7.3.2. Staff Interviews

Interviews with health professionals will take place throughout the trial duration using purposeful sampling. Most interviews will be done via telephone, although some may be done face to face (for example to coincide with an SIV observation). Taking part will be optional. For all telephone interviews, the same process regarding obtaining verbal consent will be followed as for the patient interviews. Written informed consent will be obtained for all face to face staff interviews.

7.3.3. Observations

Written informed consent for collection of qualitative data will be obtained from all staff present at the launch event site initiation visits, training sessions and recruitment clinics, prior to participation. If an individual does not wish to take part in an observation of a group activity, the researcher will not make any notes about that person or their involvement in the group. Anyone

present can ask that observations are not undertaken at any particular time and for any individual situation where, in their judgement, this course of action is not considered appropriate.

7.4. Randomisation

Consenting patients will be randomised on a 1:1 basis using permuted blocks of variable length, stratified by gender and three recognised NOSE-derived categories of baseline severity (30-50 = Moderate, 55-75 = Severe, 80-100 = Extreme,). Randomisation will be administered centrally by the Newcastle Clinical Trials Unit (CTU) secure web-based system. Site staff with the delegated responsibility of randomisation will access the web-based randomisation system with a login and password. The treatment allocation is open label and will be provided with a unique patient number to the research staff once the complete details have been entered into the system.

Participants will be randomised between:

1) Septoplasty
2) Medical management

Please see section 8 for further details on Septoplasty and Medical Management.

7.5. Trial Assessments

7.5.1. Eligibility Assessments (Only to be carried out with patient's consent)

The following assessments must be conducted/administered after the patient consents to see if they are eligible for the NAIROS study:

- Clinical Examination
- Pre-randomisation SNOT-22 score
- Pre-randomisation NOSE scale
- Age/Sex
- Intention to reduce turbinate
- Baseline recording of 4 core features including endoscopy (without decongestion):
    - The side of the convexity
    - The site of deflection (whether anterior/ posterior/upper/lower or all)
    - Endoscopy findings to look for evidence of exclusion criteria eg pus/polyps etc

- Whether the extent of the observer rated airway block by the septum is less than or greater than 50% at endoscopy

7.5.2. Assessments Pre-Randomisation

The following assessments must be conducted/administered to patients that consent to the main randomised controlled trial.

- SF-36
- Measurements of nasal patency pre and post decongestion (please see nasal patency measurements protocol for further details)
  - Peak nasal inspiratory flow rate (measured by the PNIF meter), an indication of how well air flows through the nasal airway as a whole
  - Nasal partitioning ratio (NPR), an indication of the symmetry of air flow through the nostril
- DOASS post decongestion only
- Participants' preferred contact mode (SMS message, email, telephone or letter)
- Consent for surgery if randomised to surgery

7.5.3. Eligible patients that decline the main trial

Patients that are eligible following screening but decline to participate in the main trial will be asked to consent to providing anonymised baseline comparison data for the NAIROS database.

This comprises reports of:

- SNOT22
- NOSE score
- Intention to reduce turbinates
- Baseline recording of 4 core features including endoscopy (without decongestion):
  - The side of the convexity
  - The site of deflection (whether anterior/ posterior/upper/lower or all)
  - Endoscopy findings
  - Whether the extent of the observer rated airway block by the septum is less than or greater than 50% at endoscopy

- age/sex data
- reasons for declining

This is to allow an analysis of the comparability of our trial participants to the total pool of those referred at each participating site.

The consent process will explain that those allocated to the medical management arm are asked to defer surgery for up to a 12 month review, but will also undergo interim review at six months.

7.5.4. Patients randomised to Surgery

In the surgical arm, at the time of surgery the following information will be recorded:

1. the date of surgery,
2. whether septoplasty +/- turbinate reduction was carried out
3. Whether there were any complications

Please also see section 8.1.1 for further details recorded post septoplasty. Patients will be contacted by either telephone, email or texts 2 weeks after the surgery in order for the research team to record any adverse events.

7.5.5. Patients randomised to Medical Management

At the time of randomisation, patients will be given their prescription to collect 6 months of Mometasone and saline sprays. Patients will be contacted by either telephone, email or text 2 weeks after they have been randomised in order for the research team to record any adverse events.

7.5.6. 6 months after Randomisation

The following assessments are required at 6 months following randomisation for both arms:

- SNOT-22 score*
- NOSE scale
- Record Endoscopic assessment

- Measurements of nasal patency pre and post decongestion (please see nasal patency measurements protocol for further details)
    - Peak nasal inspiratory flow rate (measured by the PNIF meter), an indication of how well air flows through the nasal airway as a whole
    - Nasal partitioning ratio (NPR), an indication of the symmetry of air flow through the nostrils
- DOASS (post decongestion)
- Adverse events
- Concomitant Medications
- Health utilisation questionnaire
- SF-36
- Face to face review/feedback on patient wellbeing

* As SNOT-22 score at 6 months is the primary outcome measure, we would like to ensure that we get the results of the questionnaire by whichever method is the most convenient way for the patient (i.e via post or email). This is only necessary if the patient is unable to make the clinic appointment at 6 months.

In the surgical arm, the 6 month review the following information will be verified:

- the date of surgery,
- whether septoplasty +/- turbinate reduction was carried out
- Whether there were any complications from the septoplasty

In the medical management arm the research team will record how compliant the patients were at taking their Mometasone and saline nasal sprays.

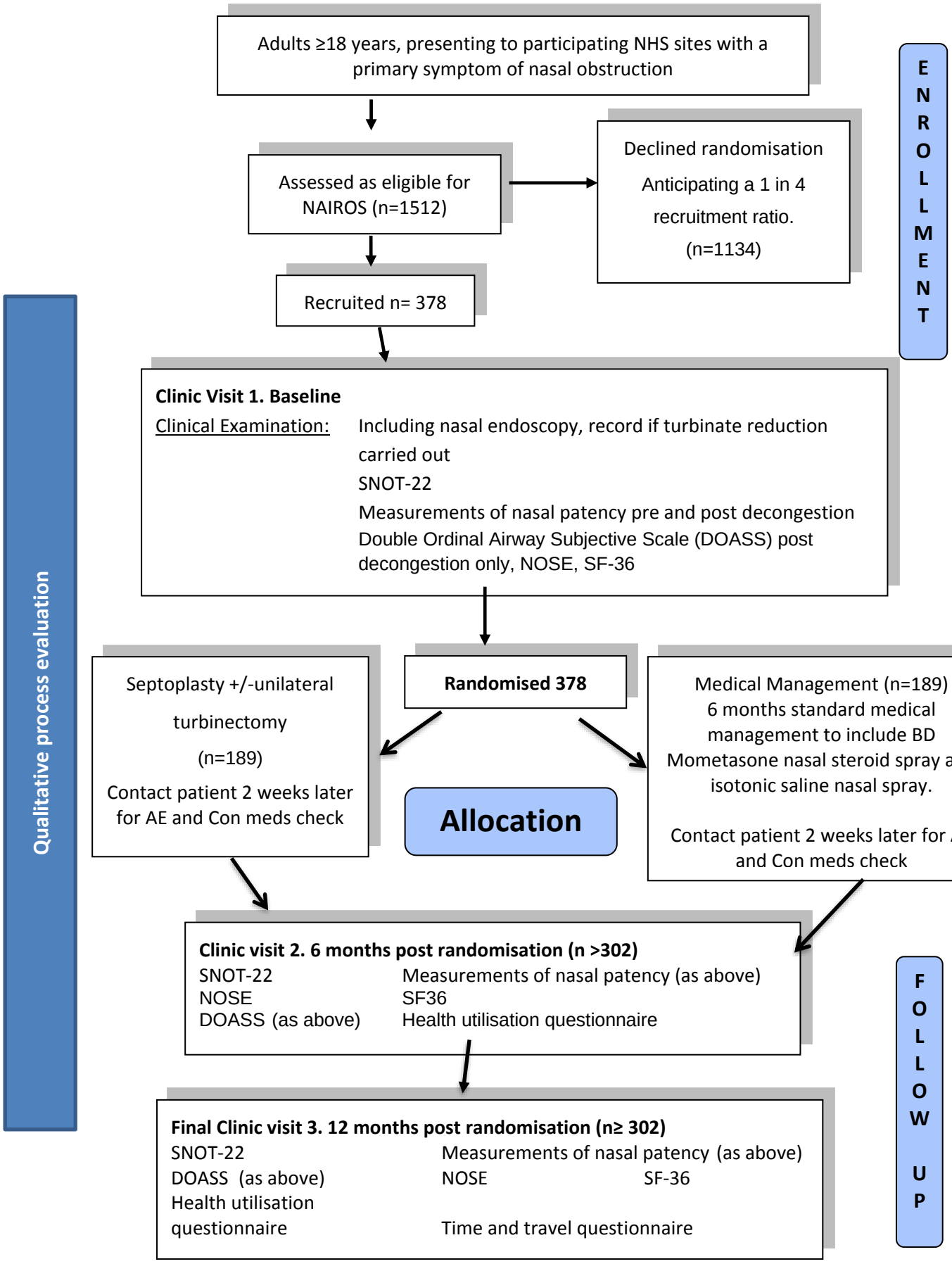
7.5.7. 12 months after Randomisation

The following assessments are required at 12 months following randomisation for both arms:

- SNOT-22 score
- NOSE scale
- Record Endoscopic Assessment
- Measurements of nasal patency pre and post decongestion (please see nasal patency measurements protocol for further details)

  - Peak nasal inspiratory flow rate (measured by the PNIF meter), an indication of how well air flows through the nasal airway as a whole
  - Nasal partitioning ratio (NPR), an indication of the symmetry of air flow through the nostrils
- DOASS (post decongestion)
- Adverse Events
- Concomitant Medications
- Health Utilisation questionnaire
- Time and travel questions
- SF-36
- Feedback on patient wellbeing

7.6. NAIROS flow diagram



7.6.1. Schedule of Events

Procedures	Pre-Screening	Screening/ Consent/ Pre-Randomisation (Visit 1)	*Contact Patient 2 weeks after randomisation (+/- 14 days)	Septoplasty (6-8 weeks later)	*Contact Patient 2 weeks after surgery (+/- 14 days)	6 months +/-2 weeks (Visit 2)	12 months +/-2 weeks (Visit 3)
Patient Information Sheet 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 & pre-randomisation					
Clinical examination Includes nasal endoscopy (without decongestion) & Baseline recording of 4 core features*		√ Post consent & pre-randomisation				√	√
SNOT-22		√ Post consent & pre-randomisation				√^	√
NOSE		√ Post consent & pre-randomisation				√	√
DOASS (post decongestion) only for patients consenting to the main trial		√ Post consent & pre-randomisation				√	√
Measurements of nasal patency see Nasal patency protocol for further information (only for patients consenting to the main trial)		√ Post consent & pre-randomisation				√	√
SF-36 (only for patients consenting to the main trial)		√ Post consent & pre-randomisation				√	√
Health Utilisation Questionnaire						√	√
Randomisation (following complete assessments)		√					
Medical Management Arm Dispensing of trial drugs (only if randomised to medical management arm) 6 month supply of saline spray & Mometasone given		√	√				
Septoplasty Arm (6-8 weeks after randomisation)				√			
Post-surgery CRF				√			
Feedback on patient wellbeing. Contact can be made via telephone, text or email.						√	√
Record technical failures from those operations where widening of the nasal airway has been achieved yet the patients' symptoms persist						√	√
Travel and time questionnaires							√
Adverse event assessments		√	√	√	√	√	√
Concomitant Medications		√	√	√	√	√	√

* 4 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 less than or greater than 50%. ^ SNOT-22 at 6 months may be collected by post or email, whichever method is the most convenient for the patient if they are unable to make the clinic appointment.

7.7. Withdrawal Criteria

Participants have the right to withdraw from i) allocated treatment and /or ii) follow up at any time without having to give a reason. Participants who withdraw from treatment will be asked to remain in follow-up as per the protocol.

Investigator sites will attempt to ascertain the reason for withdrawal on the withdrawal form and document this reason with the date and type of withdrawal (treatment, follow-up, both) within the Case Report Form and participant's medical notes.

The Investigator must discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Unacceptable toxicity from medical management
- Participant withdrawal of consent
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw
- Termination of the clinical trial by the sponsor

Participants who withdraw from the trial will not be replaced.

7.8. Storage and Analysis of Samples

No patient samples will be taken or used during this trial.

7.9. End of Trial

The end of the trial is defined as the conclusion of the last patient's last visit (i.e. the 12 month visit of the final patient recruited to the trial).

8. INTERVENTIONS

8.1. Septoplasty

Septoplasty involves the correction of nasal septal deviation +/- reduction of the inferior turbinate on the concave side. Intention to reduce turbinate will be recorded prior to randomisation.

Septoplasty is carried out in the hope of improving symptoms such as a blocked nose, snoring and sleep disturbance. Like any operation, there is a risk of complications. NAIROS Surgeons will continue to vary in their turbinate surgery, according to how they see individual patient needs. We plan to look at the changes after surgery and medical treatment according to how bad the patients' symptoms were in the first place, and if they are men or women. This will help us work out at the end of the trial – who are the people who stand to gain most from a septoplasty operation.

Participants will have a closed septoplasty, will be sutured, not packed, will be a day case (where possible). The recommended postoperative twice daily regime will be of saline douche plus Naseptin cream (or if the patient, is allergic to peanuts content of Naseptin, Bactroban ointment). Participants will be recommended to take a few days off work.

8.1.1. Surgical Assessments to be recorded at time of Surgery

Grade of Surgeon	Consultant	Associate Specialist/ Staff Grade or other
	Yes/No	Yes/No

Table 1. Grade of Surgeon performing the septoplasty

Steps of Septoplasty	Performed
Closed Approach	Yes/No
Unilateral Hemitransfixion incision	Yes/No

Unilateral Mucoperichondrial flap	Yes/No
Bilateral Mucoperichondrial flap	Yes/No
Cartilage resection	Yes/No
Cartilage scoring	Yes/No
Septal cartilage grafting	Yes/No
Maxillary crest medialised	Yes/No
Mattress sutures to close	Yes/No
Sutures to hemitransfixion incision	Yes/No
Nasal Splints	Yes/No
Nasal Packing	Yes/No

Table 2. Steps of Septoplasty

Surgery to Turbinates	Performed
Unilateral Turbinate Surgery	Yes/No
Turbinate reduced	Yes/No
Turbinate resected	Yes/No

Table 3. Surgery to Turbinates

NAIROS data analysis will separate technical failures from those operations where widening of the nasal airway has been achieved yet the patients' symptoms persist. Experienced surgeons, either consultants or non-consultant career clinicians, but not trainee otolaryngologists will deliver the NAIROS interventions to minimise the confounding of the results by poor technical performance. We will estimate and report the failure rate of septoplasty in an appropriately trained, cross-sectional cohort of surgeons. The NAIROS default is day care treatment with suture not packing. The insertion of a pack would not however count as an exclusion in this trial. Where in patient overnight stay is required, this will be documented and costed appropriately.

NAIROS is primarily a trial of the airway benefit of surgery versus medical management. Given the lack of evidence base around the turbinate on the concave side, we have site consensus that the intervention may include submucosal tissue reduction of the (mostly anterior) portion of the

inferior turbinate on the concave side, according to clinician judgement of individual patient requirements.

Intention to reduce turbinate will be recorded at recruitment.

Surgery will be carried out within 6 to 8 weeks of randomisation.

8.2. Trial Medication Medical Management Arm

The IMP for this trial is classified as a low-risk category A and as such no trial specific labelling, temperature monitoring or accountability is required. Medical management will comprise regular use of one metered dose of an isotonic nasal saline spray (Sterimar) once per day, followed by a fluorinated steroid spray (Mometasone). The steroid will be taken twice daily at 100mcg (2 puffs in each nostril twice daily) for up to 6 weeks. After 6 weeks this will reduce to 2 puffs once daily or 1 puff in each nostril twice daily, to 6-months post randomisation.

8.2.1. Mometasone fluorinated steroid spray

The SmPC for NASONEX® 50 micrograms/actuation Nasal Spray, Suspension will be used for this trial.

8.3. Drug Storage and Supply

The IMP listed above is a commercially available, UK-licensed drug taken from routine hospital stock. The IMP is not supplied by the Sponsor as a trial drug and should be ordered, stored and destroyed in the usual way according to local hospital policy. The IMP should be managed throughout the trial as standard stock i.e. for storage and destruction. Any generic brand may be used.

8.3.1. Preparation and Labelling of IMP

The IMP is available as commercial product and should be labelled in accordance with standard hospital policies. No trial specific labelling will be required.

8.3.2. Dosage Schedule & Modifications

Sterimar isotonic saline spray will be used at one metered dose per nostril twice per day for 6 months, followed by twice daily dose of 100mcg Mometasone steroid spray (2 puffs each nostril) for the first 6 weeks. After 6 weeks 100mcg dose once daily or 1 puff in each nostril twice daily for the rest of the 6 months.

8.3.3. Known Drug Reactions and Interactions

There are no known drug interactions listed on the SmPC for NASONEX® 50 micrograms/actuation Nasal Spray date of revision of text 3 May 2017. Please see section 4.4 "special warnings and precautions for use" for the known drug reactions listed on the SmPC for NASONEX® 50 micrograms/actuation Nasal Spray date of revision of text 3 May 2017.

8.3.4. Concomitant Medications

It is the responsibility of the prescribing clinician to check for interactions between trial drugs and other medications. For further guidance please refer to SmPC for NASONEX® 50 micrograms/actuation Nasal Spray date of revision of text 3 May 2017.

8.3.5. Assessment of Compliance

As a pragmatic trial using standard treatment as part of the medical management arm we shall not assess precisely any Mometasone spray residuum.

During monitoring visits the monitor will check that the patient received the 6 months' supply of Mometasone. The participants will be asked at the 6-month visit to estimate for how many months they took their Mometasone nasal spray. As the IMP has a Type A status (low-risk notification only) from the MHRA a risk-proportionate trial management and monitoring approach will be made and reviewed by sponsor, pharmacy and governance staff.

9. TRIAL DEVICES

9.1. PNIF meter (used for both arms)

The PNIF meter is a CE-marked, non-invasive medical device. It is as a Class 1 medical device, which represents the lowest category of risk.

9.1.1. PNIF Storage and Supply

The PNIF meter and its accessories should be stored within the following temperature and humidity range:- Temperature -40°C to + 60°C Humidity 20 to 80% RH non condensing. One PNIF meter will be provided to each site.

9.1.2. How to record measurements on the PNIF Meter

Full measurement instructions are given in the nasal patency measurements SOP. A training video and a SOP will be provided to each site. The operator requires minimal skill sets and repeatable measurements can be achieved from the first patient with little or no learning curve. The test is safe and completely painless for the patient, facilitating the compliance with repeat assessments at baseline, 6 and 12 months post recruitment. PNIF and NPR will be measured during the same session and the whole measurement set should take 1 to 2 hours (including 20 minutes acclimatisation, pre-decongestant measurements, between 5 and 60 minutes for decongestant to take effect, and post-decongestant measurements).

9.1.3. Known PNIF meter Device Reactions and Interactions

The disposable masks for the PNIF meter are made of a material that may cause an irritation reaction in some participants. Use of the mask should be discontinued in participants who exhibit such a reaction. The device is mechanical, not electronic, and so is not susceptible to electromagnetic radiation.

9.2. NVI Rhinospirometer (used for both arms)

The NV1 Rhinospirometer is a CE-marked, non-invasive medical device. It is a Class 1 medical device, which represents the lowest category of risk. One NV1 Rhinospirometer will be provided to each site.

9.2.1. NV1 Rhinospirometer Storage and Supply

The NV1 Rhinospirometer and its accessories should be stored within the following temperature and humidity range: Temperature -40°C to + 60°C Humidity 20 to 80% RH non condensing.

9.2.2. How to record measurements using the NV1 Rhinospirometer

Full measurement instructions are given in the nasal patency measurements protocol. A training video and a SOP will be provided to each site. The operator requires minimal skill sets and repeatable measurements can be achieved from the first patient with little or no learning curve. The test is safe and completely painless for the patient, facilitating compliance with repeat assessments at baseline, 6 and 12 months post recruitment. PNIF and NPR will be measured during the same session and the whole measurement set should take 1 to 2 hours (including 20 minutes acclimatisation, pre-decongestant measurements, between 5 and 60 minutes for decongestant to take effect, and post-decongestant measurements).

9.2.3. Known NV1 Rhinospirometer Device Reactions and Interactions

The disposable nosepieces for the NV1 Rhinospirometer are made of a material which may cause an irritation reaction in some participants. Use of the nosepiece should be discontinued in participants who exhibit such a reaction. The use of an NV1 Rhinospirometer near to sources of electromagnetic radiation, such as mobile phones, radio transmitters, x-ray equipment etc., may prevent it from functioning correctly.

9.3. Sterimar Isotonic Saline Spray (used in the medical management arm)

The “Sterimar” saline device for this trial is a CE medical device (Class IIa) and as such no specific labelling or accountability is required.

9.3.1. Sterimar Device Storage and Supply

The device listed above is a commercially available, UK-licensed device taken from routine hospital stock. The device is not supplied by the Sponsor as a trial drug and should be ordered, stored and destroyed in the usual way according to local hospital policy. The device should be managed throughout the trial as standard stock i.e. for storage and destruction. Any generic brand may be used.

9.3.2. Preparation and Labelling of Sterimar Device

The device is available as commercial product and should be labelled in accordance with standard hospital policies. No trial specific labelling will be required.

9.3.3. Dosage Schedule & Modifications

1 metred dose twice daily into each nostril

9.3.4. Known Sterimar Device Reactions and Interactions

It is the responsibility of the prescribing clinician to check for interactions between trial device and other medications.

9.3.5. Assessment of Compliance

As a pragmatic trial using standard treatment as part of the medical management arm we shall not assess precisely any Sterimar saline device residuum. The patients will be asked at the 6-month visit to estimate how many months they took their isotonic saline nasal spray.

During monitoring visits the monitor will check that the patient received the 6 months' supply of Sterimar saline device.

10. SAFETY MONITORING AND PHARMACOVIGILANCE

10.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom it is intended to administer a medicinal product or procedure, including occurrences which are not necessarily caused by or related to that medicinal product or procedure. Adverse events will be captured from the point of randomisation.

Adverse Reaction (AR)	An untoward or unintended response in a participant, which is related to the medicinal product or procedure i.e. that a causal relationship between the trial intervention and an AE is at least a reasonable possibility and the relationship cannot be ruled out. All cases judged as having a reasonable suspected causal relationship to the study intervention qualify as adverse reactions.
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at <u>immediate</u> risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. For the purposes of this study, Septoplasty specific SAEs include, but are not limited to: • Unexpected events occurring during the surgical intervention e.g. excessive bleeding, • Significant postoperative bleeding, above that normally expected following the surgical intervention • Complications related to the administration of the general anaesthetic

- Unexpected events related to septoplasty

	Note that within NAIROS, hospitalisation for elective surgery is NOT considered to be an SAE.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity or frequency of which is not consistent with the approved Reference Safety Information.

10.2. Recording and Reporting AEs and SAEs

All AEs occurring from date of randomisation to end of trial participation at 12 months (Visit 3) must be recorded in the eCRF page as well as the participant's medical notes. The severity of AE's will be assessed by the investigator as "mild/moderate/severe".

SAEs occurring from date of consent to the end of trial participation at 12 months (Visit 3) must be reported to NCTU on trial-specific SAE report form within 24 hours of the site becoming aware of the event. Should an investigator become aware of an SAE following the patient's last visit, but before the End of Trial, as defined in Section 7.9, this should also be reported to the Sponsor. All SAEs which occur as a consequence of the surgery (infections etc.) or impact from medical management arm should also be reported within 24 hours of knowledge of the event.

Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the trial.

Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected in accordance with the approved Reference Safety Information if a causal relationship is suspected

Any change of condition or other follow-up information should be submitted to the NCTU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

10.3. Recording and Reporting SUSARs

All SUSARs occurring from date of randomisation until last patient last visit and must be reported to the MHRA and REC. The Sponsor/CI or NCTU will perform this reporting.

The assessment of expectedness will be performed by the sponsor/CI against the approved Reference Safety Information (RSI) for the trial. The RSI is contained within Mometasone Reference Safety Information SOP.

Fatal and life-threatening SUSARS must be reported no later than 7 calendar days after the sponsor/CI/NCTU has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs must be reported no later than 15 calendar days after the sponsor/CI/NCTU has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a SUSAR they must contact the CI, sponsor representative and the trial manager immediately. The reporting timeframe starts at day 0 when the Sponsor/CI/NCTU is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)

- EudraCT number
- Patient trial number and date of birth
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

This information must be provided on [name of form or media of notification]. The site is expected to fully cooperate with the [Sponsor/CI/NCTU] in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

PIs will be informed of all SUSARs by the Sponsor/CI or NCTU.

10.4. Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the Reference Safety Information approved for the trial.
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness to SARs.

- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

Sponsor

- Assessment of expectedness of any SUSARs
- Expedited reporting of SUSARs to the CA and REC within required timelines
- Notification of all investigator sites of any SUSAR that occurs

TSC/DMC

- Review of safety data collected to date to identify any trends

10.5. Notification of Deaths

All deaths will be reported via the trial specific SAE form to the NCTU and sponsor. This SAE form is due immediately upon knowledge of death by the investigator site.

10.6. Pregnancy Reporting

Non-essential surgery such as septoplasty is contraindicated in pregnancy and surgery should not be performed.

There are no or limited amount of data from the use of Mometasone furoate in pregnant women. Studies in animals have shown reproductive toxicity. As with other nasal corticosteroid preparations, Mometasone Nasal Spray should not be used in pregnancy and those who become pregnant should discontinue use. Infants born of mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

In the event of a trial participant, becoming pregnant on trial the site must notify NCTU, the Chief Investigator and the sponsor representative within 24 hours of becoming aware of the pregnancy. If a patient becomes pregnant, the pregnancy must be reported as per the trial specific guidance document for pregnancy reporting and followed up until completion of pregnancy. Site must approach the trial participant or the partner of a trial participant to obtain consent to follow the pregnancy to completion.

10.7. Overdose

Inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of hypothalamic-pituitary-adrenal (HPA) axis function.

Management

Because the systemic bioavailability of Mometasone Nasal Spray is <1%, overdose is unlikely to require any therapy other than observation, followed by initiation of the appropriate prescribed dosage.

Overdoses will be recorded and notified to the sponsor by completion of a deviation report by the Trial Manager.

10.8. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU must be notified immediately and details of the USM given. The NCTU must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the [Sponsor's/NCTU's] standard operating procedures.

10.9. Development Safety Update Reports

The Development Safety Update Report will be the DSUR will be prepared by the TMG group supported by NCTU for review and completion by the CI. The Sponsor will review the final version of the report before submission to the MHRA.

11. STATISTICAL CONSIDERATIONS

The trial analysis will follow a fully detailed and approved Statistical Analysis Plan, a versioned controlled document written by the Trial Statisticians, signed by the Chief Investigator, and retained in the Statistics Trial Master File.

11.1. Analysis Populations

- Pragmatic Intention to treat (ITT) group - with all ineligible and protocol violator participants included in the analysis on an intention to treat basis with participants kept in their randomised treatment group. This will include outcome measures completed at any time.
- Compliant ITT group – all participants in the ITT group complying with questionnaires completed within the specified return window.
- Per treatment group – all randomised participants who start treatment included in the analysis according to the treatment they receive.
- Non-randomised group - those eligible to be included in the trial but declining to take part

11.2. Statistical Analyses

11.2.1. Analysis of the Primary Outcome Measure

The primary outcome measure is the post-operative SNOT-22 score at 6-months. SNOT-22 scores will be recorded at randomisation, 6 and 12 months post randomisation. The primary analysis is comparison of scores at 6-months by randomised treatment arm. The primary comparison is between participants randomised to immediate surgery vs medical management. Mean overall scores (with associated 95% confidence intervals) will be presented by treatment group. The associated significance of any observed difference will be calculated in multivariate regression models adjusting any treatment effect by stratification factors at randomisation [1) gender 2) severity at baseline (according to three NOSE categories reported in the literature: 30 – 50 “Moderate”; 55 – 75, “Severe”; 80 - 100 “Extreme”)]. Secondary analyses will also adjust for the influence of baseline severity SNOT score as a continuous covariate, planned turbinate reduction as a binary covariate and other important demographic and clinical covariates at randomisation (including but not exclusively age, BMI, smoking, endoscopic features). Non-linear relationships between continuous baseline measures and outcome will be addressed by simple and possibly more complex fractional polynomial transformation.

The NAIROS model will generate a linear predictor score of patient outcome weighted according to the statistical importance of each covariate. Each patient’s linear predictor score will be

compared against observed score for internal validation. This model will be used to explore recommendations for treatment options.

The importance of baseline severity, as a continuous distribution of NOSE score at randomisation, will be further explored graphically by Subpopulation Treatment Effect Pattern Plots (STEPP analysis[24]) to display the predicted point estimates of any treatment effect (with 95% CI) over the range of NOSE values (range 6 – 20 in NAIROS participants), further informing any patient selection guidance and recommendations.

Statistical analyses will be carried out on an intention to treat basis. The number of ineligible participants and reasons for ineligibility will be reported. A sensitivity analysis may be conducted and reported if the number of ineligible participants or crossover is excessive. Participants may switch over from medical to surgical management and the NAIROS trial anticipates that a number of participants may take up this opportunity. The implication of such crossover, which typifies surgical trials, is that the intention to treat analysis will produce a conservative estimate of the effect of septoplasty. Non-compliance (including crossover) may be addressed using an 'as treated' approach or complier average causal effect (CACE) approach, since intention to treat analysis under non-compliance is biased when the intervention effect is large [25]. Alternative analyses can provide less biased estimates [26]. Statistical methods for withdrawal of participants, based on statistical censoring, may be considered. NAIROS may undertake a per treatment (as treated) analysis where participants who crossover are 'censored' at the time of crossover corresponding to two periods of follow up pre- and post- crossover, for those participants who crossover, where the length of each follow up periods is an exposure variable. The crucial aspect to these proposed analyses is collating information on date and reason for withdrawal or crossover.

11.2.2. Analysis of Secondary Outcome Measures

Analyses of secondary outcomes will largely be descriptive.

Secondary analyses of longitudinal measures will be based on scores during the full 12-month follow-up period accounting for time. Summary statistics and graphical representation of subjective scales tabulated by arm and overall at randomisation, 6 months and 12 months follow up. Repeated measures analyses will be used to investigate the outcome scores (SNOT, NOSE, SF-36) between treatment groups over time points. Variation between participants will be included

as a random effect with an assumed normal distribution. Analysis will include the stratification factors of baseline severity and gender.

Adverse events will be tabulated according to WHO CTC AE grade version 4.03. Number of severe (CTC grade 3, 4 or 5) will be reported as a proportion of all AE. Number of participants experiencing at least one severe CTC AE will be reported as a proportion of all participants. Surgical complication/ failure and re-intervention will be tabulated and will not subject to statistical testing. Technical failures from operations where widening of nasal airway achieved yet the symptoms persist will be reported.

Clinical examination includes the 4 core features are recorded;

1) The side of convexity (laterality)
2) The side of deflection (anterior / posterior/ both)
3) Whether the extent of airway block by the septum is less than or greater than 50%
4) Whether the extent of the airway block by the septum is less than or greater than 50%

Clinical examination also includes objective measurements of nasal patency. This includes the peak nasal inspiratory flow rate (PNIF) and nasal portioning ratio (NPR) during maximal inhalation. In both cases, three measurements will be made and either the maximum (PNIF) or average (NPR) value used.

The Nasal Partitioning Ratio (NPR) is then calculated as follows;

$$NPR = V_L - V_R / V_L + V_R$$

Where V_L and V_R are the volumes inspired through the left and right nostrils respectively. The range of NPR is from -1 (left side complete obstruction) to +1 (right hand side complete obstruction). Summary statistics will be presented for PNIF and NPR by arm and overall, at baseline, 6 months and 12 months follow up.

Subjective Double Ordinal Airway Subjective Scale (DOASS) with summary statistics by arm and overall at baseline, 6 months and 12 months follow up. The subjective score of partitioning of nasal airflow between the 2 nasal passages is made by means of two different scales.

Descriptive analyses of a 100 mm visual analogue scale (VAS) with a centre point for equality to assess septal deviation.

Summary statistics and graphical representation of subjective SNOT-22 subscales (Rhinologic, Sleep, Ear/facial pain, Psychological) and tabulated by arm and overall at baseline, 6 months and 12 months follow up.

11.2.3. Planned Subgroup Analyses

Tests of heterogeneity will assess robustness of the overall treatment effect across stratification subgroups, and by intention to perform unilateral turbinate reduction.

11.2.4. Interim Analyses and Criteria for the Premature Termination of the Trial

There are no formal interim analyses of the primary outcome measure planned except for snapshots reported to DMC. DMC/TSC meetings are held annually, but may be held more frequently if requested. There are no formal statistical stopping rules.

11.3. Sample Size Calculations

Some septal surgery and septorhinoplasty studies report higher pre-operative SNOT-22 means (34.1, 36.3, and 40.0) [27-29] than others [13, 30] (20.1 and 21.5). Predictably, those with higher baseline scores report greater post-operative reduction. Buckland [28] reported a ~15 point decrease in score post-operatively, Poirrier [29] a ~19 point decrease and Phillips [27] a ~21 point decrease. Hytonen's data presentation is incomplete with apparently very wide ranges of difference averaging out at only 4 points with no distribution details, although reporting reductions in 9 of the SNOT-22 items [13]. NAIROS anticipates some benefit at 6 months from the medical management, thus the difference between the randomised groups is likely to be less than these reported effect sizes. The SNOT-22 minimal clinically important difference in the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis was 8.9 [31]. Septal surgery is reported variously as showing SNOT-22 falls above (10 points) [30] or below (4 points) this boundary [13]. In the absence of a specific figure for septoplasty MCID, NAIROS has assumed a clinically relevant reduction being at least 9 points.

Reported standard deviations (SD) were 18 [27] - in external septoplasty – to 24 [29] in septorhinoplasty, NAIROS assumes the larger, more conservative standard deviation (SD).

For an anticipated reduction of 9 points, with assumed SD of 24, the associated standardised treatment effect size estimate is 0.38. Sample size calculations are based on conservative t-test for superiority assuming equal variance across groups, despite the primary analysis being based on adjustment for stratification covariates which would increase power. The proposed total sample of 378 participants allows for 20% drop out –found to be an issue in our unit's two prior septal surgery audits [4, 32]. The retained 302 participants (151 per arm at completion), are required to show a 9-point [31] difference in overall SNOT-22 score between arms, with 90% power and 5% Type I error, assuming a SD of 24. This recruitment target is achievable and is deemed the evidence required to change clinical practice.

NAIROS will not adapt the sample size calculation based on any planned interim analysis reporting smaller SD or larger interim effect size. If the variability is less or the true effect size is larger than 9 point difference at 6 months, as hypothesized, then NAIROS will have greater power and smaller probability of false positive error as a consequence, giving the trial more credibility.

12. HEALTH ECONOMICS ANALYSIS

A 'within trial' economic analysis and longer term model will be conducted to determine the cost -effectiveness of septoplasty versus medical management over a one year time period. The perspective of the analysis will be the NHS. We shall also take a wider societal perspective by including costs borne by trial participants (e.g. time lost from usual activities, travel time and monetary costs of accessing care).

Costs will be based upon the costs of the randomised interventions received (micro costed) and costs of any adverse events. Data on surgical procedures and any subsequent adverse events will be reported on a case report form (time in theatre, time in recovery room, grade of surgeon, assistant and anaesthetist; type of anaesthesia; time in hospital). Use of subsequent primary and secondary care (GP/nurse appointments, outpatient/inpatient appointments) in the follow up period will be collected via a health utilisation questionnaire administered at 6 months and 12 months post randomisation. Patient costs and time away from usual activities will be collected on a participant time and travel questionnaire, administered at the end of the clinical follow-up period.

Data on resource use, use of services and time away from usual activities will be combined with trial specific estimates and nationally available data [33] to produce a cost for each trial

participant. From these trial participant costs, a mean cost per intervention and a mean cost taking into account patient costs will be estimated. The within trial analysis will also compare changes in health related quality of life, based on responses to the SF-36 which is most likely to be sensitive to changes in health related quality of life in this population. The SF-36 will be administered at baseline, 6 and 12 month. Responses to the SF-36 will be converted into SF-6D scores using standard algorithms [23] and used to estimate quality-adjusted life years (QALYs). Costs and outcomes beyond the trial period will be taken into consideration using a longer term economic model.

Three separate analyses will be conducted:

(1) Cost-effectiveness analysis: based on the incremental cost per adverse event [34, 35] avoided and incremental cost per change in SNOT-22 score at 12 months. Mean costs for each randomised arm will be calculated. Mean costs will be compared to mean change in adverse events and proportion of participants who have had a ≥10 point change in SNOT-22 score. In the cost effectiveness analysis these will then be presented as point estimates of mean incremental costs and effects.

(2) Cost-utility Analysis: based on incremental cost per QALY gained. SF-36 is most likely to be sensitive to change in this population (sleep domain plus reported data [27]. Recorded at baseline, 6 and 12 months. QALYs will be estimated using the area under the curve approach for each trial participant. Both mean cost and QALYs will be presented for each randomised group and incremental mean costs and QALY calculated along with the incremental cost per QALY gained.

(3) Longer term economic model: We anticipate that the surgical arm will be more costly and potentially more effective. However, the time horizon of the trial may not be sufficient for the additional benefit to offset the additional costs. Dependent on the findings of the within trial analysis we will model the longer term costs and benefits of septoplasty versus no surgery and delayed surgery.

The design of the model will be consistent with good practice guidelines [36]. The data from the trial will be the main source of data for the economic model but further data will be systematically derived from the literature. Probabilistic and deterministic sensitivity analysis will be used to address parameter and other forms of uncertainty.

For all economic analyses, deterministic sensitivity analyses will be performed to explore key uncertainties. Where appropriate these analyses will be combined with a stochastic analysis (e.g. bootstrapping). This data will be presented as point estimates and cost-effectiveness and cost-effectiveness acceptability curves (CEACs) for the CEA and CUA and longer term model.

13. QUALITATIVE ANALYSIS

All interviews will be audio-recorded, transcribed verbatim and edited to ensure anonymity of respondent. Contemporaneous field notes from non-participant observation in clinical settings will be edited to ensure anonymity of participants. Data will be managed using NVivo software. The analysis will be conducted according to the standard procedures of rigorous qualitative analysis [37] including open and focused coding, constant comparison, memoing [38], deviant case analysis [39] and mapping [40]. We will undertake independent coding and cross checking and a proportion of data will be analysed collectively in 'data clinics' where the research team share and exchange interpretations of key issues emerging from the data. Audio-recorded recruitment consultations will be subjected to content, thematic, and novel analytical approaches, including targeted conversation analysis [41] and quanti-qual appointment timing (the 'Q-Qat method' [42]), as described in the QuinteT Recruitment Intervention protocol [2]. There will be a focus on aspects of information provision that is unclear, disrupted, or potentially detrimental to recruitment and informed consent.

14. DATA HANDLING

14.1. Data Collection Tools and Source Document Identification

Data including the number of participants screened, approached and interested in taking part will be collected via a log completed by site staff conducting screening.

Trial data for each individual patient will be collected by each site's PI or their delegated person and recorded in the electronic case report form (eCRF) in the clinical data management software package (MACRO^{TM}) for the trial. Patient identification on the eCRF will be through a unique trial identifier number allocated at the point of randomisation. A record linking the patient's name to the unique trial identifier number will be held only in a locked room at the trial site, and is the responsibility of the PI. As such, participants cannot be identified from eCRFs. The CI or delegated person will monitor completeness and quality of data recording in eCRFs and will correspond

regularly with site PIs (or their delegated team member) with the aim of capturing any missing data where possible, and ensuring continuous high quality of data.

Participants will complete the paper assessment tools as required. The tools will also only be identified using the same unique patient identifier number. Data will be entered at sites into the secure online system (MACRO™), with the paper originals remaining at site.

Audio-recordings of recruitment/consent discussions will contain patient identifiable information. The original recordings will be encrypted and password protected and sent to Newcastle University where selected recordings will be transcribed using purposeful sampling.

14.2. Data Handling and Record Keeping

Overall responsibility for data collection lies with the CI. Data collected on paper assessment tools will be entered onto a secure validated clinical data management system (MACRO™) at sites. Clinical data will be entered into the database (MACRO™) remotely at each site by the local investigator or another member of the site research team with delegated responsibility for this activity. A unique trial number is allocated at randomisation and will be used to identify participants on all paper data collection forms throughout the duration of the trial. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. The quality and retention of trial data will be the responsibility of the CI. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy. The MACRO™ database is an electronic data capture system which complies with the requirements of regulatory bodies and maintains an audit trail of any changes to the data. All data stored in MACRO™ benefit from Elsevier's hosting service in collaboration with Rackspace which features redundancy and backup measures in case of disaster.

Audio-recordings, with consent, will be transcribed verbatim and edited to ensure anonymity of respondent. Contemporaneous field notes from non-participant observation in clinical settings will be edited to ensure anonymity of participants. Qualitative data will be managed using NVivo software.

14.3. Access to Data

Staff involved in the conduct of the trial, including the PIs, Trial Management Group and NHS staff involved in screening and intervention will have access to the site files. Password limited access,

restricted to own particular role and site to the trial's MACRO™ database will be granted to site's PIs and their delegated data entry personals at these sites. NCTU trial management team will have a monitor role access to the trial's MACRO database for all sites for monitoring purposes.

Clinical information shall not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the DMC or the REC. Secure anonymised electronic data will be released to the trial statistician for statistical analyses. The PI and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.4. Archiving

Data will be archived in accordance with the NCTU SOP and European Commission Directive 2005/28/EC Article 17. Essential data will be retained for a period of at least 10 years following close of trial in line with sponsor policy and the latest Directive on GCP (2005/28/EC). Archiving will be authorised by the Sponsor following submission of the end of trial report. Authorisation will be requested from the Sponsor to destroy the documentation at the end of the archiving period.

Research participants will be protected through the removal of personal, confidential and sensitive data. In addition to data files (rendered as csv-delimited text), data list files will provide descriptions of all variables, including how each variable was constructed and calculated where appropriate.

The CI will be the data custodian.

15. MONITORING, AUDIT & INSPECTION

Monitoring of trial conduct and data collected will be performed by a combination of central review, site monitoring visits and an external Data Monitoring Committee and Trial Steering committee to ensure the trial is conducted in accordance with GCP. Trial site monitoring will be undertaken by Newcastle CTU. The main areas of focus for site specific monitoring will include

consent, serious adverse events, data completeness and accuracy relating to the primary and secondary outcomes, and essential documents in Investigator Site Files.

Site monitoring will include:

- All original consent forms will be reviewed as part of the trial file. The presence of the consent form in the ISF and patient notes will be confirmed for 100% participants. Original consent forms will be compared against the trial participant identification list.
- All reported serious adverse events will be verified against treatment notes/medical records (source data verification).
- The presence of essential documents in the ISF and trial files will be checked.
- Source data verification of primary endpoint data and eligibility data for a number of participants (this number will be determined by the NCTU risk assessment which will be documented in the monitoring plan) entered in the trial.

Central monitoring will include:

- Confirmation of the presence of essential documentation and relevant approvals

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The trial may be subject to audit by representatives of the Sponsor or inspection by MHRA/HTA. Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

Aggregated data will be analysed by the Trial Statisticians and reported to an external independent DMC and TSC at least annually. The data will be analysed in open and closed sessions according to the DMC Charter, as agreed with the DMC members at the start of the trial.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Research Ethics Committee Review and Reports

The CI/NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

Newcastle CTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The Sponsor/NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

A progress report will be submitted annually to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

16.2. Peer Review

The trial has undergone external peer review as arranged by the NIHR HTA as part of the funding process. The protocol has been reviewed and authorised by the sponsor, funder, Chief Investigator, co-applicants, Senior Trial Manager and Senior Statistician.

16.3. Public and Patient Involvement

A patient and public involvement (PPI) group has been involved in the design and planning of the trial from the start. The ongoing role of the PPI panel will be to refine our recruitment strategy, to continue to inform adequacy and accessibility of patient information and convey their views to the TSC and Principal Investigators. A member of the PPI panel will also participate in the TSC meetings.

16.4. Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

The NCTU will obtain a Clinical Trial Authorisation from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment.

The NCTU will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by the NCTU until the end of the trial.

The NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

16.5. Protocol Compliance

It is the responsibility of the CI to ensure that the clinical trial is run in accordance with GCP and the protocol.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Unintentional protocol deviations will be documented and reported to the Sponsor in accordance with NCTU SOPs. Deviations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach.

16.6. Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The NCTU will notify the MHRA and the NHS REC within the required timelines in accordance with the NCTU SOP.

16.7. Data Protection and Patient Confidentiality

All investigators and trial staff must comply with the requirements of the Data Protection Act 1998 with regards to collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis.

16.8. Indemnity

The sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial. This indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantive employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial. The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access participants and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts, e.g. General Practitioners will provide their own professional indemnity.

16.9. Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and trial procedures must not be changed without the mutual agreement of the CI, Sponsor, Trial Management Group and Trial Steering Committee where appropriate.

Substantial amendments will be submitted to the REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by the NCTU.

16.10. Post-Trial Care

Standardised care – e.g., continued use of steroids and saline as per local clinical decision. Or referral for surgical consideration as per local clinician decision.

16.11. Access to the Final Trial Dataset

The TSC, DMC, trial statistician, data manager and other members of the central trial team as required will have access to the full trial dataset. The full trial dataset will not be available to individual site investigators prior to publication of the main trial results. Site investigators will be allowed to access the full dataset after publication of the main trial results if a formal request describing their plans is approved by the TSC.

17. DISSEMINATION POLICY

The results of the trial will be presented at topic-specific national or international conferences and published in a general medical journal with the monograph published by HTA. Authorship of all publications will be on a named individual authorship basis. For each publication all individuals who fulfil the authorship definition for the publishing journal or site will be included as individually named authors. Authorship order will be decided by the Chief Investigator and TMG.

A lay summary of results will be available on the NAIROS website. Access to the HTA report will also be available through the trial website. Members of the PPI focus groups will review results and they will be involved in writing lay summaries of results for dissemination to relevant patient groups.

18. REFERENCES

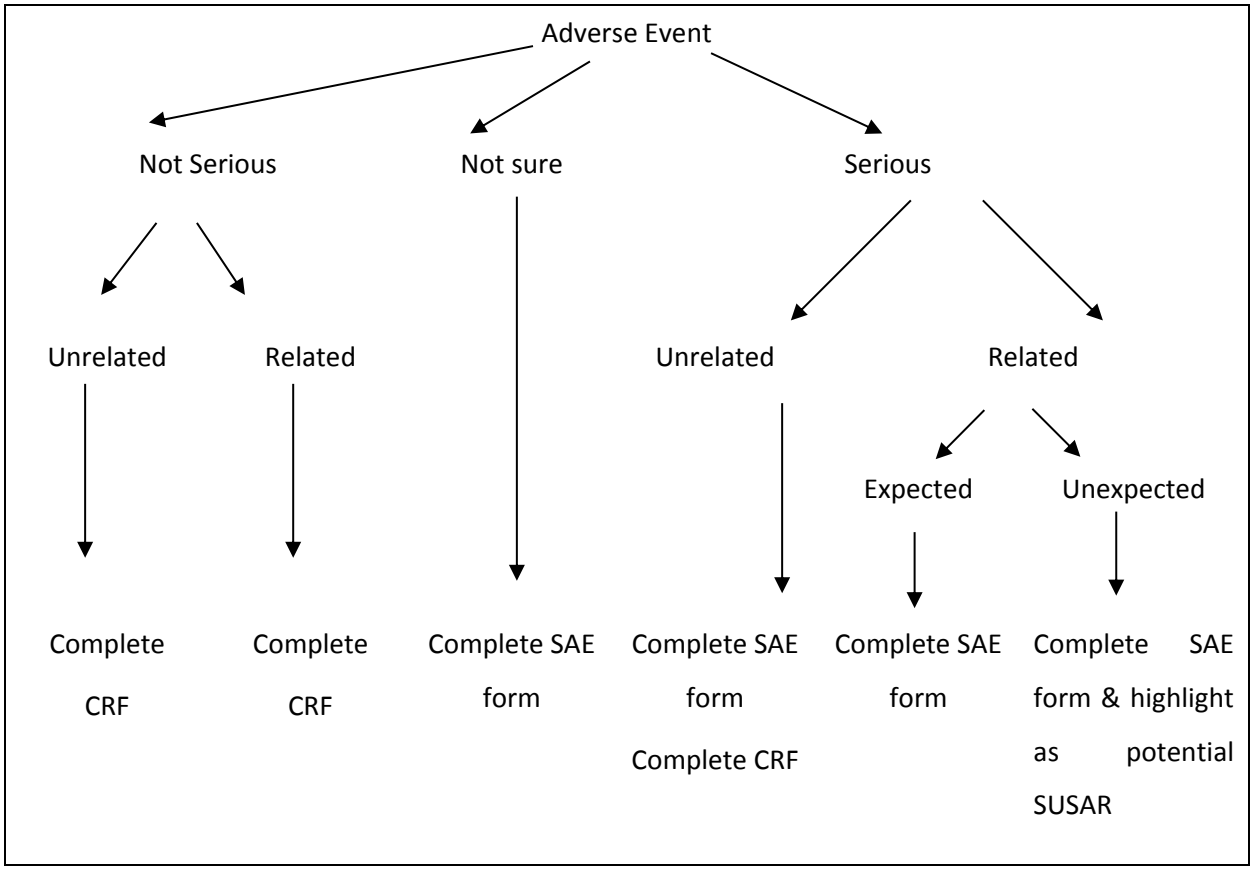
1. *Hospital Episode Statistics data.*
2. Donovan, J.L., et al., *Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI).* Trials, 2016. **17**(1): p. 283.
3. Rhee, J.S., et al., *A systematic review of patient-reported nasal obstruction scores: defining normative and symptomatic ranges in surgical patients.* JAMA Facial Plast Surg, 2014. **16**(3): p. 219-25; quiz 232.
4. Enache, A., A. Lieder, and W. Issing, *Nasal septoplasty with submucosal diathermy to inferior turbinates improves symptoms at 3 months postoperatively in a study of one hundred and one patients.* Clin Otolaryngol, 2014. **39**(1): p. 57-63.
5. Akduman, D., et al., *Patients` evaluation for the surgical management of nasal obstruction.* Rhinology, 2013. **51**(4): p. 361-7.
6. Gandomi, B., A. Bayat, and T. Kazemei, *Outcomes of septoplasty in young adults: the Nasal Obstruction Septoplasty Effectiveness study.* Am J Otolaryngol, 2010. **31**(3): p. 189-92.
7. Haroon, Y., H.A. Saleh, and A.H. Abou-Issa, *Nasal soft tissue obstruction improvement after septoplasty without turbinectomy.* Eur Arch Otorhinolaryngol, 2013. **270**(10): p. 2649-55.
8. Kimbell, J.S., et al., *Computed nasal resistance compared with patient-reported symptoms in surgically treated nasal airway passages: a preliminary report.* Am J Rhinol Allergy, 2012. **26**(3): p. e94-8.
9. Toyserkani, N.M., T. Frisch, and C. Von Buchwald, *Postoperative improvement in acoustic rhinometry measurements after septoplasty correlates with long-term satisfaction.* Rhinology, 2013. **51**(2): p. 171-5.
10. Lipan, M.J. and S.P. Most, *Development of a severity classification system for subjective nasal obstruction.* JAMA Facial Plast Surg, 2013. **15**(5): p. 358-61.
11. Boyce, J.M. and R. Eccles, *Assessment of subjective scales for selection of patients for nasal septal surgery.* Clin Otolaryngol, 2006. **31**(4): p. 297-302.
12. Michels Dde, S., et al., *Nasal involvement in obstructive sleep apnea syndrome.* Int J Otolaryngol, 2014. **2014**: p. 717419.
13. Hytonen, M.L., et al., *Does septoplasty enhance the quality of life in patients?* Eur Arch Otorhinolaryngol, 2012. **269**(12): p. 2497-503.
14. Low, W.K., *Can snoring relief after nasal septal surgery be predicted?* Clin Otolaryngol Allied Sci, 1994. **19**(2): p. 142-4.

15. Neumann, A., et al., *[Patients' satisfaction after nasal septal and turbinate surgery. Results of a questionnaire].* Laryngorhinootologie, 2007. **86**(10): p. 706-13.
16. Ertugay, C.K., et al., *Is septoplasty effective on habitual snoring in patients with nasal obstruction?* Eur Arch Otorhinolaryngol, 2015. **272**(7): p. 1687-91.
17. Owens, D., et al., *The accuracy and reproducibility of rhinospirometry in detecting flow asymmetry in a nasal cavity model.* Eur Arch Otorhinolaryngol, 2011. **268**(10): p. 1469-74.
18. Cuddihy, P.J. and R. Eccles, *The use of nasal spirometry as an objective measure of nasal septal deviation and the effectiveness of septal surgery.* Clin Otolaryngol Allied Sci, 2003. **28**(4): p. 325-30.
19. Fyrmpas, G., et al., *The value of bilateral simultaneous nasal spirometry in the assessment of patients undergoing septoplasty.* Rhinology, 2011. **49**(3): p. 297-303.
20. 2016, M.S.D.L., *Nasonex 50 micrograms/actuation Nasal Spray, Suspension.*
21. Sastre, J. and R. Mosges, *Local and systemic safety of intranasal corticosteroids.* J Investig Allergol Clin Immunol, 2012. **22**(1): p. 1-12.
22. Donovan, J., et al., *Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult.* BMJ, 2002. **325**(7367): p. 766-70.
23. Brazier, J., J. Roberts, and M. Deverill, *The estimation of a preference-based measure of health from the SF-36.* J Health Econ, 2002. **21**(2): p. 271-92.
24. Bonetti, M. and R.D. Gelber, *Patterns of treatment effects in subsets of patients in clinical trials.* Biostatistics, 2004. **5**(3): p. 465-81.
25. Dumville, J.C., D.J. Torgerson, and C.E. Hewitt, *Reporting attrition in randomised controlled trials.* BMJ, 2006. **332**(7547): p. 969-71.
26. Ye, C., et al., *Estimating treatment effects in randomised controlled trials with non-compliance: a simulation study.* BMJ Open, 2014. **4**(6): p. e005362.
27. Phillips, P.S., et al., *Functional and cosmetic outcomes of external approach septoplasty.* Am J Rhinol Allergy, 2011. **25**(5): p. 351-7.
28. Buckland, J.R., S. Thomas, and P.G. Harries, *Can the Sino-nasal Outcome Test (SNOT-22) be used as a reliable outcome measure for successful septal surgery?* Clin Otolaryngol Allied Sci, 2003. **28**(1): p. 43-7.
29. Poirrier, A.L., et al., *Is the Sino-Nasal Outcome Test-22 a suitable evaluation for septorhinoplasty?* Laryngoscope, 2013. **123**(1): p. 76-81.

30. Pannu, K.K., S. Chadha, and I.P. Kaur, *Evaluation of benefits of nasal septal surgery on nasal symptoms and general health.* Indian J Otolaryngol Head Neck Surg, 2009. **61**(1): p. 59-65.
31. Hopkins, C., et al., *Psychometric validity of the 22-item Sinonasal Outcome Test.* Clin Otolaryngol, 2009. **34**(5): p. 447-54.
32. Arunachalam, P.S., et al., *Nasal septal surgery: evaluation of symptomatic and general health outcomes.* Clin Otolaryngol Allied Sci, 2001. **26**(5): p. 367-70.
33. Curtis, L., *Unit Costs of Health and Social Care.* 2014.
34. Makitie, A., et al., *Postoperative infection following nasal septoplasty.* Acta Otolaryngol Suppl, 2000. **543**: p. 165-6.
35. Becker, S.S., et al., *Revision septoplasty: review of sources of persistent nasal obstruction.* Am J Rhinol, 2008. **22**(4): p. 440-4.
36. Velasco, L.C., L.M. Arima, and R.S. Tiago, *Assessment of symptom improvement following nasal septoplasty with or without turbinectomy.* Braz J Otorhinolaryngol, 2011. **77**(5): p. 577-83.
37. Rapley, T., *Some Pragmatics of Data Analysis.* Silverman D, ed. Qualitative Research: Theory, Method & Practice. London: Sage, 2010.
38. Glaser, B., *The constant comparative method of qualitative analysis.* Social Problems, 1965. **12**: p. 436-45.
39. Seale, C., *The Quality of Qualitative Research.* London: Sage, 1999.
40. Charmaz, K., *Constructing Grounded Theory: A Practical Guide through Qualitative Analysis.* Thousand Oaks, California. : Sage;, 2006.
41. Wade J, D.J., Lane JA, Neal DE, Hamdy FC, *It's not just what you say, it's also how you say it: opening the 'black box' of informed consent appointments in randomised controlled trials.* Social science & medicine, 1982. **68**: p. 2018-28.
42. Paramasivan, S., et al., *A simple technique to identify key recruitment issues in randomised controlled trials: Q-QAT - Quanti-Qualitative Appointment Timing.* Trials, 2015. **16**: p. 88.

19. APPENDICES

19.1. Appendix 1 - Safety Reporting Diagram



Contact details for reporting SAEs and SUSARs

Please send SAE form via [Fax number]

Or call

0191 208 2519 Monday to Friday 8am-4:30pm

19.2. Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made