NATTINA

The **NA**tional **T**rial of **T**onsillectomy **IN** **A**dults: a clinical and cost effectiveness study

Protocol

Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne, NE7 7DN.

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2. Protocol Signature Page

2.1 Protocol Authorisation Signatories

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Signature ……..…… Date ……..…

Mr Tony Fouweather , Statistician

Signature ……..…… Date ……..……

Dr Lesley Hall, Senior Trial Manager

2.2 Principal/Chief Investigator Signature

I confirm that I have read and understood protocol version 4.0 dated 18/08/2016. I agree to comply with the study protocol, the principles of Good Clinical Practice (GCP), research governance, clinical trial regulations and appropriate reporting requirements.

Signature ……..…….. Date ….……..…

Print Name ……..……..…

Site Name/I.D. ……...

Contents

3. Glossary of Abbreviations

Abbreviation	Definition
A&E	Accident and Emergency
AE	Adverse Event
AUC	Area Under the Curve
CET	Clinical Evaluation and Trials
CI	Chief Investigator
Co-I	Co-Investigator
CRC	Clinical Research Collaboration
CSP	Coordinated System for gaining NHS Permission
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DVD	Digital Versatile Disc
eCRF	Electronic Case Report Form
ENT	Ear, Nose and Throat
EOI	Expression of Interest
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
ICF	Informed Consent Form
IVR	Interactive Voice Response
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator

PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
RCT	Randomised Controlled Trial
RDS	Research Design Service
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SF-12	Short Form-12 Health Survey
SIGN	Scottish Intercollegiate Guideline Network
SMS	Short Message Service
SOP	Standard Operating Procedure
STAR	Sore Throat Alert Return
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TOI 14	Tonsillectomy Outcome Inventory 14
TSC	Trial Steering Committee

4. Responsibilities

Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study.

Funder: The Health Technology Assessment (HTA) Programme (Ref No: 12/146/06) is funding this study. Contact at HTA: Alexa Cross, Programme Manager, National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, University of Southampton, Alpha House, Enterprise Road, Southampton SO16 7NS. Email: a.cross@southampton.ac.uk.

Trial Management: The study will be managed through the Newcastle Clinical Trials Unit (NCTU); a UK Clinical Research Collaboration (CRC) registered Clinical Trials Unit (CTU). A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The TMG will consist of Prof Janet Wilson (CI), James O'Hara (Co-I), Dr Scott Wilkes (Co-I), Dr Nikki Rousseau (Health Research Methodologist), Dr Katie Haighton (Qualitative Research Lead), Dr Deborah Stocken (Deputy Director Newcastle Clinical Trials Unit), Dr Lesley Hall (Senior Trial Manager), Alexander von Wilamowitz-Moellendorff (Trial Manager), Rebecca Harrison (Trial Manager), Prof Luke Vale (Health Economist), Tara Homer (Health Economist), Tony Fouweather (Statistician) and Amy Collins (Project Secretary).

The day-to-day management of the trial will be co-ordinated by the Trial Managers.

Principal Investigator: The Principal Investigator will have overall responsibility for the conduct of the study at a particular trial site.

Trial Management Responsibilities:

The following functions falling under the responsibility of the sponsor will be delegated to Professor Janet Wilson as Chief Investigator:

- Ethics Committee Opinion (including application for Research Ethics Committee (REC) favourable opinion, notification of protocol amendments and end of trial, site specific assessment and local approval).
- Research and Development (R&D) Approval (including application for global checks, via NIHR CSP).
- Good Clinical Practice and Trial Conduct (including GCP arrangements, data monitoring, emergency and safety procedures).
- Administration of funding for the study.

Trial Conduct at Site

Investigator Responsibilities:

- Study conduct and the welfare of study subjects.
- Familiarity with the study interventions.

- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events.
- Screening and recruitment of subjects.
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event.
- Obtaining local approval and abiding by the policies of Research Governance.
    - Assistance will be provided by the Trial Manager.
- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, the Data Protection Act and any other relevant legislation and regulatory guidance.
- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- The Principal Investigator (PI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed and dated curriculum vitae as evidence for the Trial Master File (TMF).
- Ensuring Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintaining study documentation and compliance with reporting requests.
- Maintaining an Investigator Site File, including copies of study approval, list of subjects and their signed Informed Consent Forms (ICFs).
- Documenting appropriate delegation of tasks to other study personnel e.g. Research Nurse, Co-Investigator(s), Trial Coordinators, Data Managers.
- Ensuring data collected is accurate, timely and complete.
- Providing updates on the progress of the trial.
- Ensuring subject confidentiality is maintained during the project and archival period.
- Ensuring archival of study documentation for a minimum of 5 years following the end of the study, unless local arrangements require a longer period.

5. Protocol Summary

Short title:	The NAtional Trial of Tonsillectomy IN Adults (NATTINA): a clinical and cost effectiveness study
Protocol version:	4.0
Protocol date:	18/08/2016
Chief Investigator:	Professor Janet Wilson
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	Health Technology Assessment, Clinical Evaluation and Trials
Study design:	A multi-centre, randomised, controlled surgical trial with internal pilot.
Study intervention:	1:1 randomisation of immediate tonsillectomy versus conservative management (i.e. deferred surgery).
Primary objective:	To compare the effectiveness (as number of sore throat days) and efficiency of tonsillectomy versus nonsurgical management for recurrent acute tonsillitis over a 24 month period.
Secondary objectives:	i) Clinical Effectiveness: • To compare other metrics of sore throat severity including responses on the Tonsil Outcome Inventory 14 (TOI 14) and STAR (Sore Throat Alert Return) data for any sore throat episodes experienced • To compare quality-of-life (QOL) as recorded by SF-12 longitudinally during study follow up. • To report the number of adverse events, visits to the GP/walk-in clinic/A&E, prescriptions issued and additional interventions required for sore throat and related events through STAR data, and supported by data linkage to primary care patient records. • To adjust the estimate of effectiveness in the light of other baseline covariates including severity of tonsillitis • To evaluate the impact of alternative sore throat patient pathways by observation and statistical modelling of outcomes

- To assess to what extent trial participants are representative of the total population of sore throat patients referred to Ear Nose Throat (ENT) clinics

ii) Economic Evaluation:

- To compare quality-adjusted life years (QALYs) using the Area Under the Curve (AUC) method based upon SF-6D scores derived from the SF-12 responses measured at baseline, throughout the study and during any episodes of sore throat experienced.
- To compare the cost-effectiveness measured in terms of the incremental cost per sore throat day avoided from the perspective of the NHS and patients over 24 months
- To compare the cost-utility based on incremental cost per QALY gained from the perspective of the NHS and participants over 24 months
- To compare the cost-benefits based on the perspective of the NHS and participants' willingness to pay to avoid a sore throat day using the NATTINA contingent valuation questionnaire 'Value of Avoiding a Sore Throat Day' administered at baseline.

iii) Qualitative Process Evaluation: To document the views, experiences and acceptability of patients and clinicians regarding tonsillectomy and conservative management, and how patient experience may shape future research required

vi) Future Research: To propose further research questions using newfound cost-benefit information to develop algorithms that guide and assess management of health services.

Primary outcome:	Total number of sore throat days over the 24 months following randomisation.
Number of study sites:	9
Study population/size:	72 patients will be recruited and randomised during the internal pilot study. A further 438 patients will be recruited during the full trial. 510 patients will be recruited in total.
Study duration:	57 months

6. Background

6.1 Background

The role of tonsillectomy in the management of adult sore throat remains uncertain, and despite demonstrable compliance with Scottish Intercollegiate Guidelines Network (SIGN) guidance [1], UK regional variation in tonsillectomy rates persists [2]. The 2009 Cochrane review [3] identified only one evaluable adult trial with just 70 participants [4] over 90 days' follow-up, and concluded that reasonable levels of evidence were only available for children. Currently there is evidence for increasing numbers of admissions for severe or complicated tonsillitis (e.g. peritonsillar abscess) as the number of tonsillectomy operations has fallen over the past decade in England [5]. Sore throats cost the NHS over £120 million per annum – an estimated £60 million of this for General Practitioner (GP) consultations and medical therapy [6]. From 2011-12 in England alone secondary care costs included an estimated £10 million for bed usage and around £20 million in elective adult tonsillectomy [6].

The questions that patients, doctors and healthcare providers wish to answer relate to the relative costs and benefits of tonsillectomy against conservative management and whether there can be more refined surgical indications to maximise such benefits and hence minimise the risks.

Decision making for tonsillitis is mostly undertaken in primary care where there is greatest potential for evolution in patient pathway. Tonsillectomy is a painful procedure [7] which requires an average of 14 days off work [8, 9] and has a number of less common but intrusive complications [10], including changes in taste and tongue sensation [11, 12]. Thus, irrespective of its relative merits as a treatment, like all surgical intervention it needs to be weighed carefully against the conservative alternatives.

Antibiotic overuse in unselected community populations with viral pharyngitis is costly for health care providers [13] and efforts to try to curtail antibiotic prescription in general practice are on-going [14]. However, different economic considerations apply in those selected patients with more frequent and incapacitating episodes [1]. A comparison of immediate, versus no, versus delayed antibiotic prescribing was examined over 15 years ago in a substantial UK RCT (Randomised Controlled Trial) which found the main effect of antibiotic use was the promotion of medical consultation for sore throat [15]. However the study population in that trial included substantial numbers of children [16], and the criteria for prescription were not all aligned with the Centor Clinical Prediction Rule. More importantly in the context of NATTINA, however, the trial related to individual index episodes of sore throat. NATTINA concerns the management of patients >16 years who have had a significant disease burden, for some considerable qualifying period of time such that both they and their referring physician feel the tonsillectomy may be justified.

The NAtional Trial of Tonsillectomy IN Adults (NATTINA) consists of an internal pilot and definitive 9 centre trial with a substantial sample size of 510 adults. Participants are randomly split into two groups - surgery and conservative management. Our previous experience of a randomised trial of tonsillectomy in children [17, 18], together with other published Ear, Nose and Throat surgical trials, highlighted the problem of retaining participants in the nonsurgical cohort, especially in a trial population who were reviewed only by postal survey and diary return. These findings along with patient and public engagement have influenced the trial design and decision to use deferred surgery as the conservative management option rather than no surgery. NATTINA also keeps the research team more closely engaged with the participants through 2 face-to-face clinic visits during follow up and therefore improves

compliance rates and minimise patient cross-over. The NATTINA patient involvement forum also maintains patient engagement.
There has been no known previous attempt to map the current NHS referral criteria against any other metrics of severity. NATTINA factors in more specific and sensitive modelling of disease severity which encourages patients to apply a simple but validated estimate of sore throat severity. Current UK surgical practice is governed by SIGN guidance [1] which has hitherto been audited only to measure compliance, not validity. By carefully modelling the costs and consequences and setting these against surrogates of baseline severity, patients, clinicians, and health service funders will be presented with a range of options as to what should be the preferred threshold for surgical intervention.

A prospective result of the information generated from NATTINA is that more severely affected individuals, who will ultimately gain most from tonsillectomy, are more likely to be systematically and accurately characterised at an earlier stage, thus maximising the cost efficiency of any surgical intervention by more timely and precisely indicated intervention. Most adult tonsil disease and surgery impacts on economically active age groups, with individual and societal costs through loss of earnings and productivity. Patients will therefore benefit from more timely and efficient management – with less time lost from work or studies, and fewer days' illness. The NHS will gain through lower costs with avoidance of unnecessary operations, as well as society through conservation of productivity in an economically active patient population.

6.2 Patients

Participants will be adult patients with acute tonsillitis who have been referred to otolaryngology outpatient clinics for recurrent sore throat.

6.3 Treatment Choice

In NATTINA, referral of patients to ENT by GPs for consideration of tonsillectomy follows the current standard care pathway according to NICE guidelines. Consenting participants who are eligible for elective tonsillectomy are randomly allocated to one of two arms; elective surgery (identical to that in standard care) and conservative management.

6.4 Measuring Treatment Response

Number of sore throat days

All participants submit weekly feedback on the number of sore throat days experienced over the previous 7 days.

TOI 14 and SF-12 questionnaires

Participants will complete six monthly questionnaire packages; Tonsillectomy Outcome Inventory 14 (TOI 14) and SF-12 which refer to their throat symptoms and quality of life.

The TOI 14 is a validated disease-specific instrument for measuring health-related quality of life and our experience of using the TOI 14 in 3 centres pre and post tonsillectomy equips us to 1) precisely estimate the effect size of tonsillectomy; 2) estimate the spectrum of baseline severity of those referred from primary care for consideration for surgery; 3) account for such variation in the design and analysis of the trial; 4) evaluate the impact of alternative sore throat patient pathways by observation and statistical modelling of outcomes. 'Preop' was removed from the TOI 14 title for the participant questionnaires and Comparison Data Form

as they will be used both before and after surgery. The TOI 14 text size and spacing has been marginally modified in the Comparison Data Form so as to ensure it is more user friendly for respondents.

Sore Throat Alert Return (STAR)

A subject who experiences a sore throat is asked to submit a NATTINA STAR – Sore Throat Alert Return comprising:

i. Information on the severity category of sore throat days (mild/moderate/severe)

ii. Report of over-the-counter and prescription medications used

iii. The nature of any professional healthcare advice sought if any (including GP, walk in clinic, pharmacist etc.)

iv. Number of hours unable to undertake usual activities (including time off work and studies)

v. An additional SF-12 relative to the episode

The STAR questionnaire can either be returned electronically or as a paper envelope using the free post envelopes. If participants have not returned STAR forms for several weeks the Trial Mangement Team will send a reminder letter to participants asking them to return the missing forms.

7. Research Objectives

The purpose of the study is to establish the clinical and cost effectiveness of tonsillectomy compared with conservative management for adult tonsillitis which, through observation and statistical modelling of outcomes, will evaluate the impact of alternative sore throat patient pathways and develop future research.

7.1 Internal Pilot Objectives

The following criteria are required for a successful internal pilot which will permit the main trial to go forward:

- 6 screening clinics established
- Target combined activity of 396 eligible patients screened in 6 months
- Target minimum n=72 patients randomised

The internal pilot will be considered unsuccessful if one or more of the above criteria are not met.

The internal pilot will assess the ability to recruit, in addition to:

i) Ascertain if all trial processes, including patient identification, eligibility criteria, randomisation and data collection, work as intended and the eligibility criteria are cohesively operational.

ii) Gauge more precisely the number of potential eligible patients identified in NATTINA screening clinics.

iii) Investigate referral, recruitment and acceptability across baseline severity spectrum.

iv) Identify barriers to patient recruitment and suggest improvements to impact on recruitment rates.

v) Measure patient compliance with the proposed weekly submission of number of sore throat days, plus STARs during sore throat episodes.

vi) Identify any major emerging systematic differences between recruited patients and those who decline to participate.

vii) Collate and report reasons for participation/ineligibility/decline.

viii) Quantify missing data and measure attrition in sore throat data.

7.2 Main Trial - Primary Objective:

To compare the effectiveness (as number of sore throat days) and efficiency of tonsillectomy versus nonsurgical management for recurrent acute tonsillitis over the 24 months following randomisation.

7.3 Main Trial - Secondary Objectives:

i) Clinical Effectiveness:

- To compare other metrics of sore throat severity including responses on the Tonsil Outcome Inventory 14 and STAR data for any sore throat episodes experienced.
- To compare quality-of-life as recorded by SF-12 longitudinally during study follow up.
- To report the number of adverse events, visits to the GP/walk-in clinic/A&E, prescriptions issued and additional interventions required for sore throats and related events through STAR data, and supported by data linkage to primary care patient records.
- To adjust the estimate of effectiveness in light of other baseline covariates including severity of tonsillitis.
- To evaluate the impact of alternative sore throat patient pathways by observation and statistical modelling of outcomes.
- To assess to what extent trial participants are representative of the total population of sore throat patients referred to ENT clinics.

ii) Economic Evaluation:

- To compare QALYs using the AUC method based upon SF-6D scores derived from the SF-12 responses measured [24] at baseline, throughout the study and during any episodes of sore throat experienced.
- To compare the cost-effectiveness measured in terms of the incremental cost per sore throat day avoided from the perspective of the NHS and patients over 24 months
- To compare the cost-utility based on incremental cost per QALY gained from the perspective of the NHS and participants over 24 months
- To compare the cost-benefits based on the perspective of the NHS and participants' willingness to pay to avoid a sore throat day using the NATTINA contingent valuation questionnaire 'Value of Avoiding a Sore Throat Day' administered at baseline

iii) Qualitative Process Evaluation: To document the views, experiences and acceptability of patients and clinicians regarding tonsillectomy and conservative management, and how patient experience may shape future research required

iv) Future Research: To propose further research questions using newfound cost-benefit information to develop algorithms that guide and assess management of health services.

8. Study Design

This is a multi-centre, randomised, controlled surgical trial incorporating an internal pilot. Participants will be randomised on a 1:1 basis to 2 groups using a variable block stratified design.

Subsequent to successful completion of the pilot study objectives, the main trial will commence and continue recruitment for a further 18 months.

8.1 Intervention Groups

1) Immediate tonsillectomy

2) Conservative management – i.e. deferred surgery with usual care

More details on the intervention groups can be found in section 12.

8.2 Qualitative Process Evaluation of Pilot and Main Trial

An embedded qualitative study will gather rich data on acceptability of the treatments, unforeseen consequences and perceptions of research materials and procedures in the NATTINA context. This aims to establish feasibility of provision within NHS costs.

Recruiting otolaryngologists will invite a sample of trial participants plus a sample of those who decline to participate, to consent to an in-depth interview with a researcher at a time and location convenient for them. Interviews will cover expectations and motivations for participating, experience of the treatment arm and views about sore throat.

ENT staff and GPs will also be interviewed on their experience and views.

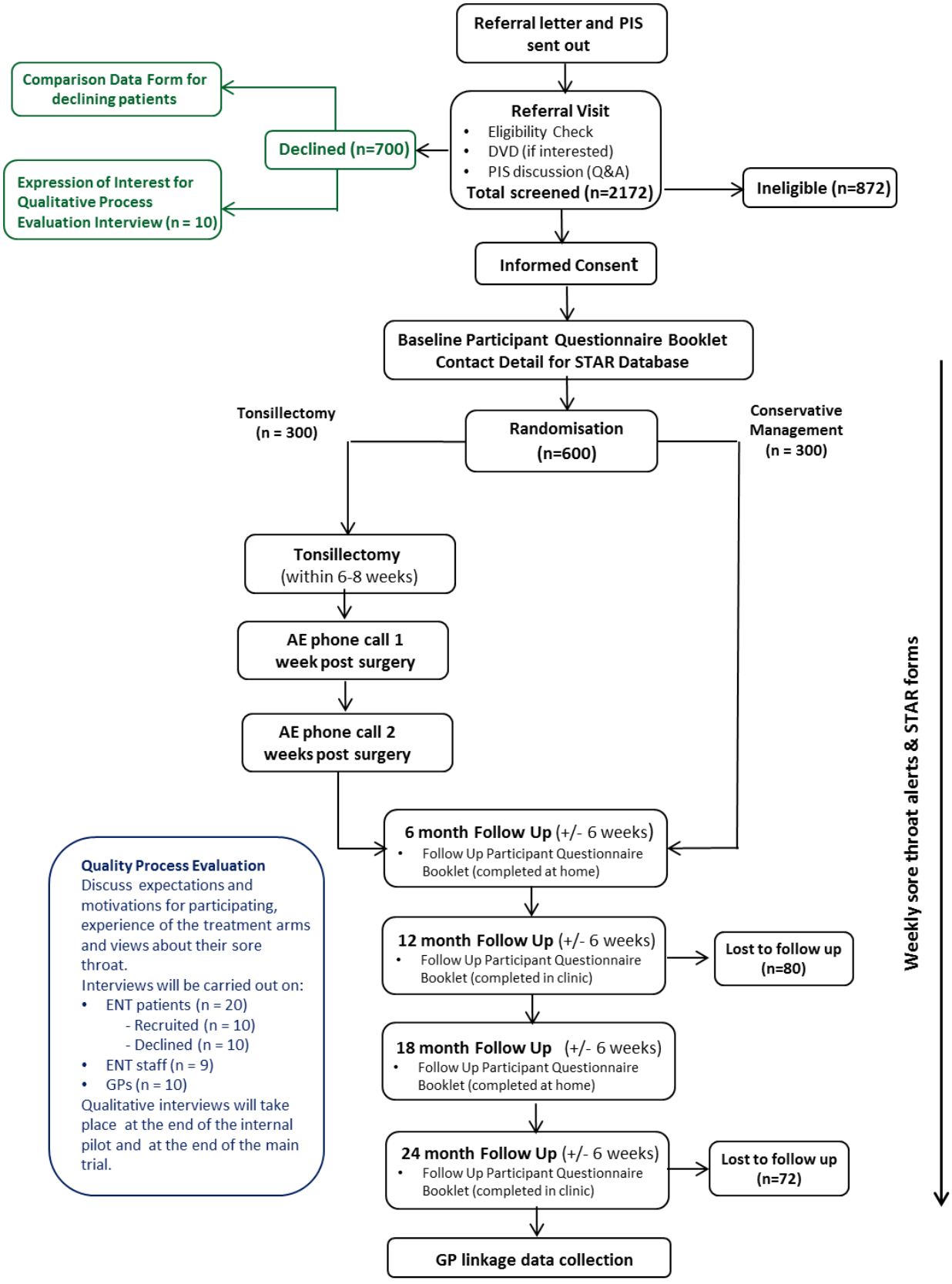
More details can be found in sections 11.1, 14.1 and 14.3.

8.3 Collection of Primary Care Linkage Data

With the participant's permission, GP records will be accessed to collect primary health care usage data. This linkage data will allow the capture of adverse events, number of contacts with primary and secondary healthcare services, prescribing information and other relevant material to support data retrieved from STAR data and post-operative research nurse telephone calls.

More details can be found in sections 14.1 and 14.3.

8.4 Study Pathway



8.5 Sample Size and Duration of Study

Internal pilot recruitment:

We will initially set up 3 proposed participating sites – Newcastle, Sunderland and Dundee to start recruiting in week one of the internal pilot, shortly followed by another 3 pilot sites – Bradford, Glasgow and Aberdeen. 72 patients will be recruited at the 6 sites over a period of 6 months.

The pilot study will be considered a success if all 6 sites are set up and recruiting, with an average target throughput of 11 eligible subjects screened per centre per month and acceptability of randomisation. The process will be overseen by the Data Monitoring Committee (DMC) and the Trial Steering Committee (TSC) prior to consideration by the HTA who will decide whether to release the full funding and continue with the main study phase.

Full trial recruitment:

A further 3 research sites will be set up – Birmingham, London and a third site yet to be identified. 438 participants will be recruited over a further 18 months at the 9 sites. A total of 510 participants will be recruited throughout the study. Depending on trial progression, additional sites may be set up to aid recruitment.

Interviews for the Qualitative Process Evaluation will be carried out on a group of patients, staff and GPs during the internal pilot and towards the end of the main trial. 9 otolaryngology staff, 10 GPs and 15-20 ENT patients, including both recruited and declining patients, will have an in-depth qualitative interview with a researcher.

Follow up:

Participants will be followed up for 24 months from randomisation.

8.6 Primary Outcome Measure:

The number of sore throat days collected through weekly 'returns' from the participants over a period of 24 months will be the primary outcome measure. The data will allow comparison of tonsillectomy versus conservative management to determine the effectiveness in recurrent adult tonsillitis.

8.7 Secondary Outcome Measures:

- Responses on the Tonsil Outcome Inventory 14 (TOI14) and STAR data to measure frequency, severity, health and economic impact of any sore throat episodes experienced.
- Quality-of-life as recorded by SF-12 longitudinally during study follow up.
- Quality-adjusted life years using the AUC method based upon SF-6D scores derived from the SF-12 responses [24] measured at baseline, throughout the study and during episodes of sore throat experienced.
- The number of adverse events, visits to the GP/walk-in clinic/A&E, prescriptions issued and additional interventions required as collected from GP records and other primary care linkage data.
- Incremental cost per sore throat day avoided from the perspective of the NHS and patients over 24 months to measure the cost effectiveness.

- The views and experiences of patients and clinicians regarding tonsillectomy and conservative management and how patient experience may shape any future research required.

8.8 Definition of End of Study:

The end of the study will be the date of the last participant's 24 month follow up visit and once all SAEs have been followed up.

The trial may close earlier on the basis of new safety information, or for reasons given by the DMC/TSC, Sponsor, REC or funder.

9. Participant Population

Participants will be adult patients with recurrent acute tonsillitis who have been referred by their GP to secondary care.

9.1 Inclusion Criteria

- Age ≥ 16 years
  - Recurrent sore throats which fulfil current SIGN guidance [1] for elective tonsillectomy. *Sore throats are due to acute tonsillitis*
  - *The episodes of sore throat are disabling and prevent normal functioning*
  - *Seven or more well documented, clinically significant, adequately treated sore throats in the preceding year or*
  - *Five or more such episodes in each of the preceding two years or*
  - *Three or more such episodes in each of the preceding three years.*
- Subject has provided written informed consent for participation in the study prior to any study specific procedures

9.2 Exclusion Criteria

- Under 16 years of age
- Previous tonsillectomy
- Listed directly (i.e. added to waiting list without prior elective ENT outpatient appointment) during emergency admission (e.g. due to peritonsillar abscess/quinsy)
- Primary sleep breathing disorder
- Suspected malignancy
- Tonsilloliths (as primary referral)
- Pregnant or breastfeeding
- Bleeding diathesis (including haemophilia, sickle cell disease and platelet dysfunction)
- Therapeutic anticoagulation
- Inability to complete self-reported questionnaires and sore throat returns

10. Screening, Recruitment and Consent

10.1 Identification and Screening of Participants

Identification

The Principal Investigator and Co-Investigators will ensure all physicians are informed about NATTINA. The clinical team at the participating sites will identify patients who have been referred by a GP for consideration of tonsillectomy and will post a Participant Information Sheet (PIS) along with an invitation letter and their appointment letter if appropriate. The PIS will outline details of the study and how to watch the NATTINA information DVD on the website if they wish.

In some areas there will be participant identification centres (PICs) set up to refer to a local NATTINA trial site. Patients attending a PIC site for a tonsillectomy consultation will be given a PIS and will be invited to contact the NATTINA site if they are interested in participating in the study. Interested participants will then be invited for screening at their nearest NATTINA trial site.

Screening

Screening will be performed on all patients who attend an ENT referral clinic visit with recurrent sore throat. Screening is defined as the assessment of the NATTINA eligibility criteria at the patient's clinic visit. Potential participants who were posted a PIS will be shown the information DVD at their referral visit (unless already viewed online) and given the opportunity to discuss the study with the designated member of the research team. Inclusion and exclusion criteria will be checked and eligible patients invited to participate in the trial.

A screening and recruitment log will be kept by the investigator to document all subjects who have attended a referral visit and their outcome status (recruited, declined participation or screen failed). Reasons for ineligibility should be documented in the notes and screening log. The right to refuse to participate without giving reasons must be respected. The log will also ensure potential participants are only approached once.

Declining patients:
Patients who are eligible but decline to participate will be invited to provide anonymised baseline comparison data for the NATTINA database (age, gender, an estimate of number of sore throat days over the prior 6 months and a TOI 14 questionnaire). This will allow an analysis of the comparability of our trial participants to the total pool of those referred, at each of the 9 sites. Declining patients will also be invited to participate in a qualitative interview with a researcher. More details can be found in section 14.1.

10.2 Recruitment & Consent Procedures

Participants must be given reasonable time (minimum of 24 hours) to decide whether or not they would like to participate. Those who weren't given a Participant Information Sheet before their clinic visit will receive a minimum of 24 hours to consider, and will be invited to attend a later appointment to consent. Eligible patients wishing to take part will provide written informed consent by signing and dating the Informed Consent Form, which must be witnessed, signed and dated by a member of the research team with documented, delegated responsibility to do so. The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. A copy will also be faxed to the NCTU to monitor consent adequacy.

Each site is responsible for the provision of interpreting services for interested patients who require them and this should go through local NHS arrangements. Emphasis is placed on

finding the most direct form of communication for individual patients and encompasses spoken/written language, and those with differing audio or visual requirements.

Written informed consent should always be obtained prior to randomisation and prior to study specific procedures.

10.3 Interventions

Randomisation into an intervention group will be in a 1:1 ratio. Full details of the allocation method are given in section 13. There are 2 intervention groups:

1) Tonsillectomy: Surgery preferably within six weeks, and no more than 8 weeks, following randomisation (tonsillectomy method at the discretion of the participating centres).

2) Conservative management: i.e. deferred surgery with usual care. Participants entering the conservative arm are asked to defer surgery for up to 2 years, and will be asked to consent on the understanding that they will be reviewed at 12 months and assessed on their willingness to remain in the delayed surgery cohort. Participants will have to fulfil the SIGN guidance at the point of review to be considered for tonsillectomy. Conservative arm participants will receive the standard care, as normally treated by the patients themselves or by the referring GPs in their current practice, which typically comprises self-administered analgesia plus/minus ad hoc primary care prescription of antibiotics, attendance at walk-in centres or accident and emergency department for more severe episodes. Participants will be given the option to cross over to the tonsillectomy arm at any point in the study, SIGN guidance permitting.

10.4 Early Termination

Participants withdrawing from the study should continue follow up and their data collected unless it is against their wish. If the patient wishes to withdraw from the study as well as follow up, no further data will be collected however any data gathered prior to withdrawal will be retained.

The Research Ethics Committee, Data Monitoring Committee/Trial Steering Committee, Sponsor or funder may, at any time point during the study and for any reason, decide to close NATTINA earlier than intended.

11. Randomisation

A blocked allocation (permuted random blocks of variable length) system will be used to allocate subjects to the 2 intervention groups; tonsillectomy versus conservative management, in a 1:1 ratio stratified by centre and severity. Randomisation will be administered centrally via the NCTU using a secure web-based system, accessed by the PI or delegated individual. Patient initials, date of birth, date of consent and severity category will be entered into the web-based system, which will return the allocation status. The patient's severity category is determined by the total TOI 14 score from the Baseline Questionnaire Package, as follows:
Mild = 0 to 35
Moderate = 36 to 48
Severe = 49 to 70

Participants will be informed of their allocated treatment group following randomisation. Randomisation will allocate the patient a unique participant ID which is to be used on all CRFs and questionnaires front covers.

Designated members of staff who will be randomising patients at the participating sites will be provided with login details.

Contact details for Randomisation

Randomisation service website: **https://apps.ncl.ac.uk/random/**
(available 24 hours a day)

If you experience any problems using the randomisation system and need help or advice, please contact: 0191 208 8024 (normal office hours)

12. Study Data

12.1 Visits

Screening & Baseline visit (Referral visit) – consent and randomisation

Patients who received a PIS in advance of their referral visit will discuss the trial in detail with the clinician or other delegated investigator and any questions will be answered. Inclusion and exclusion criteria will be checked and eligible patients will be invited to participate in the study and provide informed consent. Written informed consent will be witnessed, signed and dated by the PI or co-investigator on the delegation log. Participation in the study should be clearly documented in the patient notes and on the screening and recruitment log.

A copy of the consent form is to be faxed to NCTU on the following number:
0191 580 1106

For patients who were provided with a PIS at the referral visit, or in the event the patient requests more time to consider, a second suitable outpatient appointment will be arranged for the baseline visit and to consent if wished.

Once written approval has been given, a baseline questionnaire package will be provided to the participant to complete and return to the research nurse on the same day. The questionnaire package includes:

- 'About You'
- TOI 14
- SF-12
- 'Value of avoiding a sore throat day'
- Health service utilisation

The clinical team will need to calculate the total TOI 14 score from the baseline questionnaire package in order to randomise the participant via the NCTU online randomisation system. This TOI 14 score will indicate which severity category (mild/moderate/severe) the patient should be assigned to when being randomised.

Participants randomised to immediate tonsillectomy will undergo surgery within 6 weeks of randomisation (and no later than 8 weeks).

It is recommended that the delegated responsible person taking consent should advise women of child-bearing potential not to get pregnant or try to get pregnant between consenting and undergoing surgery.

A 'participant contact details form' will be completed after randomisation and returned to Newcastle University who will use these contact details to post the 6 and 18 month study

questionnaires to the participant for completion at home. The participant's name and email address/mobile phone number will also be passed on to a responsible independent company for the sole purpose of sending out weekly sore throat alert prompts and STARs via the participant's preferred method of communication.

Declining Patients:
Patients who, following screening, are eligible but decline to participate will be invited to provide anonymised baseline comparison data for the NATTINA database. This comprises age, gender, an estimate of number of sore throat days over the prior 6 months and a TOI 14 questionnaire.
Declining patients will also be invited to an in-depth interview with a researcher from Newcastle University as part of the Qualitative Process Evaluation. These interviews will give the patients an opportunity to discuss their expectations and motivations for participating, experience of the treatment arms and views about their sore throat. Those who are interested or would like more information will complete an 'expression of interest' (EOI) form to hand back to the research team at their clinic visit. This form will be returned to the NCTU team in the pre-paid envelopes provided who will contact the patient and arrange an interview at a time and location convenient for them. Written informed consent will be obtained at the beginning of the interview.

Patients that decline the main study should be documented on the screening log.

Surgery (within 6-8 weeks)

In the event a participant is randomised to undergo a tonsillectomy but surgery is delayed due to severe tonsillitis or other complications, the participant should remain in the trial and continue to follow the surgery pathway.

Details of the surgery, including date and any complications experienced up to 30 days after the tonsillectomy will be documented in the eCRF.

Weekly throughout 24 month follow up - submissions of number of sore throat days

All NATTINA participants are prompted weekly by their preferred method of communication (SMS message, email or Interactive Voice Response [IVR] via telephone) to submit the number of sore throat days experienced in the previous 7 days. Participants are instructed that when they experience a sore throat they should submit a NATTINA 5 point design – Sore Throat Alert Return (STAR). The STAR comprises:

- Information on the severity grade of the sore throat a) mild, b) moderate (limiting instrumental activities of daily living, c) severe (limiting self-care activities of daily living and ability to swallow)
- Use of any over-the-counter and prescription medications
- The nature of any professional healthcare advice sought (if any)
- Number of hours when unable to undertake usual activities (including work/studies)
- An additional SF-12 relative to the episode

Only 1 STAR form needs to be completed per 7 days, regardless of the number of sore throat days experienced within that week. This can be completed on the supplied paper STAR forms and then sent to NCTU in the provided pre-paid envelopes or via the electronic STAR form link.

1 week and 2 weeks after surgery

The research nurse will contact the participant twice after their tonsillectomy to check on their recovery and ask if they have experienced any adverse events immediately after, or during recovery from, a tonsillectomy. Only participants who had surgery will be contacted. AEs and SAEs will be recorded as detailed in section 19.

Interim point 1 – 6 month follow up (+/- 6 weeks)

Participants will receive a questionnaire package in the post at 6 months to self-complete at home. No face-face clinic visit is needed. The questionnaire pack at 6 months will be sent out centrally by Newcastle University and comprises:

- TOI 14
- SF-12
- Health service utilisation questionnaire

Clinic visit 1 – 12 month follow up (+/- 6 weeks)

All participants are reviewed in the outpatient clinic at 12 months post randomisation, which allows in the surgical arm, a cross-check of the precise date of surgery. Participants in the conservative therapy (deferred surgery) group will be assessed on their willingness to remain in the deferred group. The 12 month clinic visit review consists of:

- Questionnaires:
  - TOI 14
  - SF-12
  - Health service utilisation questionnaire

Interim point 2 – 18 month follow up (+/- 6 weeks)

Participants will receive a questionnaire package in the post at 18 months to self-complete at home. No face-face clinic visit is needed. The questionnaire pack at 18 months will be sent out centrally by Newcastle University and comprises:

- TOI 14
- SF-12
- Health service utilisation questionnaire
- Participant time and travel questionnaire

Clinic visit 2 – 24 month follow up (+/- 6 weeks)

All participants are reviewed in the outpatient clinic at 24 months. This is the final review. Participants in the conservative therapy (deferred surgery) group will be asked whether they wish to go forward for tonsillectomy. The 24 month clinic visit review consists of:

- Questionnaires:
  - TOI 14
  - SF-12
  - Health service utilisation questionnaire

All interim point questionnaires completed at home are to be returned to the Newcastle Clinical Trials Unit in the pre-paid and addressed envelopes provided. All clinic visit

completed questionnaires should be entered on to the database by site staff and stored securely at site.

12.2 Table of Events

Time	Referral/Baseline Visit		Sore Throat Returns	Surgery	1 week after surgery	2 weeks after surgery	Interim Point 1 – Follow Up	Clinic Visit 1 - Follow Up	Interim Point 2 – Follow Up	Clinic Visit 2 - Follow Up
	Basic assessment of eligibility and interest	**Confirmation of eligibility, consent and randomisation**								
	Screening	**Consent and Randomisation**	**Weekly - Baseline to 24 months**	**Within 6-8 Weeks of baseline**			**6 months** (+/-6 weeks)	**12 months** (+/-6 weeks)	**18 months** (+/-6 weeks)	**24 months** (+/-6 weeks)
Study discussed/ PIS given/Watch DVD	X									
Informed consent		X								
Comparison data and/or EOI for Qualitative Process Evaluation (declining participants only)	X									
Baseline Participant Questionnaire		X								
Randomisation		X								
Sore throat return (and STAR if applicable) *Sent out centrally			X							
Tonsillectomy				X						
Post-operative telephone calls					X	X				
Follow-up Participant Questionnaire							X	X	X	X

12.3 Qualitative Process Evaluation

Recruiting otolaryngologists will invite a sample of trial participants plus a sample of those who decline to participate to consent to an in-depth interview. Permission for the recruited participant to be contacted for an interview will be sought when the patient consents to the pilot or main study. Patients who have declined participation will be informed about the interviews by the clinical team and invited to complete an expression of interest and or TOI-14 questionnaire.

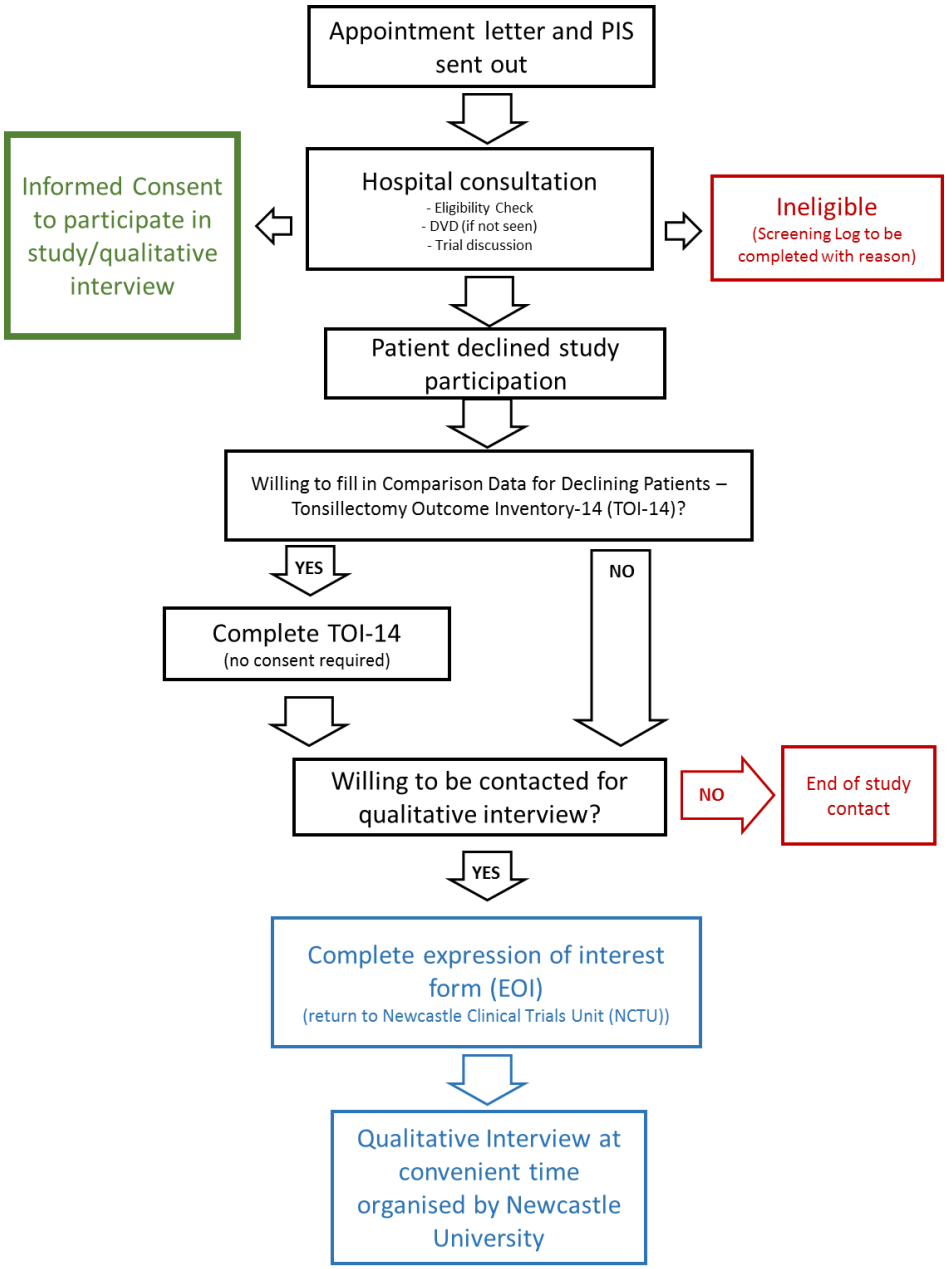


Figure 1 Flowchart for qualitative process evaluation

Recruiting staff (otolaryngologists, research nurses, nurse practitioners, clinic managers) and a sample of primary care clinicians will also be invited to participate in an interview to explore the practicality and suitability of the treatments, research tasks and randomisation, and any barriers or enablers to treatment delivery. Interviews will take place during the internal pilot and again towards the end of the main trial.

12.4 Primary Care Linkage Data

Consent will be sought to access participants' GP health records in order to gather primary health care service data at the end of their 24 month follow up. Data collected will cover the participants 24 month follow up and 12 months prior to randomisation (36 months).

The following data will be collected for each participant:

- Adverse events
- Attendance to GP/walk in clinic/A&E for sore throat or related event
- Hospitalisations and emergency referrals
- Prescriptions issued
- Any additional interventions required

12.5 Data Collection and Record Keeping

Data will be recorded by authorised staff and stored in MACRO; a secure web-based eCRF system run by the Newcastle Clinical Trials Unit. Data transferred from site to the secure validated database by remote access will be encrypted and have restricted and limited access. Analysis of this data will be undertaken by the NCTU. Subjects will be identified by a unique participant ID allocated by the randomisation system which will be used on CRFs and questionnaire front covers.

Personal details (full name, address, email address and phone numbers) will be stored on secure and restricted databases at the NCTU on the Newcastle University server for the purpose of sending out weekly sore throat alert prompts, STARs and follow up questionnaires centrally.

All interviews will be audio recorded and transcribed verbatim. Anonymous audio files and transcripts will be stored electronically and will be kept alongside other study data.

Professor Janet Wilson as CI has overall responsibility for all data collection and management. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Caldicott approval will be sought during set up at each participating site to enable the collection and transfer of patient information as part of this study. The quality and retention of study data will be the responsibility of the Chief Investigator. All study data will be archived for 5 years and in accordance with GCP and the NCTU Standard Operating Procedures.

13. Statistical Considerations

13.1 Statistical Analysis

The primary outcome measure of the total number of sore throat days experienced over the 24 months of follow-up will be analysed using negative binomial regression in order to compare the change between the NATTINA arms while adjusting for potential confounders including the stratification variables used - recruiting centre (as a random effect) and baseline severity (as a fixed effect). This analysis will be undertaken on an intention to treat basis, however patients may switch over from conservative to surgical management. In the NATTINA design, patients are asked to commit to "deferred surgery". We anticipate that a number of patients will take up this opportunity to switch to surgery. The implication of such crossover, which typifies surgical trials, is that the intention to treat analysis will produce a very conservative estimate of the effect of tonsillectomy. We will therefore also undertake an

"as treated" analysis with repeated measures corresponding to two periods of follow up for those patients who crossover from medical management to tonsillectomy. The length of these follow up periods will be as an exposure variable in the negative binomial regression.

QoL scores based on the SF-12 will be calculated according to the scoring manual at baseline and 6, 12, 18 and 24 months post randomisation. The scores will be analysed using models developed for longitudinal data. The dependent variable will be the quality of life score for an individual patient at a particular occasion. Both variation between patients and variation between occasions nested within patients will be modelled as random effects with a normal distribution. Differences between groups and changes over time will be modelled as fixed effects. The analysis will be adjusted for the differences between strata.

The analysis of other secondary outcomes will follow a broadly similar strategy; repeated measures will be analysed using a random effects model with an appropriate error structure. Should data be found to be non-Normally distributed, the use of transformations or non-parametric approaches will be considered.

The true effect of tonsillectomy is likely to lie between the estimate from the intention-to-treat analysis which is the most parsimonious account, due to anticipated cross over into surgery, and the as treated analysis, which will tend to maximise the effect size of any surgical intervention. Outcome data analysis will be at the end of the study and for DMC review and will follow a full statistical analysis plan developed prior to the start of analysis. Safety data will not be subject to statistical testing. Data with missing observations due to loss to follow-up will be examined to determine both its extent and whether it is missing at random or is informative. If data is missing to a sufficient extent, the use of appropriate multiple imputation techniques will be considered. In the event of incomplete follow up on our primary outcome for some patients we will fit an appropriate exposure variable in the regression model.

Secondary analysis will include estimation of the effects of tonsillectomy adjusted for potentially important clinical and demographical variables.

13.2 Economic Analysis

A 'within trial' economic analyses will be carried out from the perspective of the NHS, but we will also take a wider perspective by including costs borne by the participants (including time lost from usual activities due to sore throat and time, travel and monetary costs of accessing care). Costs will be based upon the costs of the randomised interventions received and on the use of subsequent care and services. Data on surgical procedures will be reported on a case report form (time in theatre; grade of surgeon, assistant and anaesthetist; type of anaesthesia; time in hospital); use of subsequent primary and secondary care (outpatient appointments), patient costs and time away from usual activities per each type of episode of care will be collected on a participant completed questionnaire at 18 months. A micro costing exercise will be conducted to elicit the other resources required to estimate the costs of the surgical procedures. Data on resource use, use of services and time away from usual activities will be combined with study specific estimates and nationally available data [19] to produce a cost for each trial participant. When appropriate, discounting will be applied to costs and outcomes at UK recommended rates [20]. From these trial participant costs, a mean cost per intervention and a mean cost taking into account patient costs will be estimated.

(1) cost-effectiveness analysis, based on the incremental cost per sore throat day avoided. Mean costs for each randomised arm will be calculated as will mean days of sore throat. In the cost-effectiveness analysis these will then be presented as point estimates of mean

incremental costs and effects (reduced sore throat days) and the incremental cost per sore throat day avoided.

(2) cost-utility analysis, based on incremental cost per QALY gained. QALYs will be based upon responses to the SF-12 converted into SF-6D scores using a standard algorithm [24]. The SF-12 will be completed at scheduled time points and because sore throat is an episodic health condition the SF-12 is included in the STAR return which patients submit at the time of a sore throat. QALYs, based upon SF-6D scores 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.

For both the cost-effectiveness and cost-utility analyses the results will be presented as point estimates of mean incremental costs and effects as well as in stochastic analyses plots of cost and effects and cost-effectiveness acceptability curves.

(3) cost-benefit analysis, cost-benefit analysis expresses both costs and benefits in commensurate units which enables comparison to be made between strategies [21]. The decision rule for cost-benefit analysis is therefore relatively simple, if the benefits measured in sterling (£) exceed the costs, this represents a gain in welfare and the strategy is deemed worthwhile [22]. Days of sore throat avoided may be difficult for policy makers to determine and measures of QALYs may not fully capture individuals' preferences to avoid days of a sore throat. An alternative technique is to use a contingent valuation method to allow patients to state their preferences, in of monetary values [23], to avoid a sore throat day. Contingent valuation will collect individuals' expression, for a given level of income, of their willingness to pay for a reduction in the number of sore throat days, with higher monetary values indicating that they would derive greater benefit. These data will be elicited in a participant completed questionnaire administered at baseline. The precise form of the questionnaire (and hence its analysis) will be determined during pilot work conducted during the study. But for each randomised group we will calculate mean willingness to pay and explore how valuations might vary according to participant characteristics (e.g. family income, gender, age, etc.). The data on the willingness to pay for a sore throat day avoided will be combined with information on number of sore throat days experienced and on the cost per participants. The results will be presented as point estimates and in stochastic analysis plots of cost and mean willingness to pay and incremental net benefit curves.

For all economic evaluations deterministic sensitivity analyses will be performed to explore key uncertainties e.g. valuations of time away from usual activities; sub-groups, etc. Where appropriate these analyses will be combined with a stochastic analysis with the results presented in the same ways as described above.

13.3 Sample Size Calculation

The total number recruited will be 510 including 72 in the internal pilot. By recruiting 510 patients we are allowing for a total loss to follow up of 25% over 24 months. 382 patients in total two groups of 191 patients (providing complete data at two years) gives 90% power to detect an effect size of 0.33 (corresponding mean intergroup difference of 3.6 days of sore throat based on a pooled estimated standard deviation of 10.8 days) assuming a type 1 error rate of 5%. The sample size calculations take account of the anticipated losses as well as predicted switch rates. We anticipate that our loss to follow-up rate should be less than the stated 25%, as we shall intensively follow-up trial participants in both arms.

Sampling for the Qualitative Process Evaluation will be purposive, seeking maximum variety in terms of age, gender, phase of trial (pilot/main) and treatment arm (including participants

who cross over). Sample size will be determined by reaching data saturation, estimated to occur at around 20 ENT patient interviews, 9 ENT staff interviews and 10 GP interviews.

14. Compliance, Withdrawal and Cross-over

14.1 Assessment of Compliance

Where feasible, visit windows of +/- 6 weeks should ensure sufficient time is offered to facilitate scheduling appointments; non-attendance for study visits will prompt follow-up by telephone. Participants may also be contacted via telephone by the research nurse at the participating site to remind or encourage them to return questionnaires or weekly alerts. Source data verification will be performed by the Trial Manager at each participating site.

14.2 Withdrawal/Cross-over of Participants

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw participants from the study intervention if he/she judges this to the in the patient's best interests. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

There are 2 options for participants in the Immediate Tonsillectomy group:

1. Cross over to conservative management before receiving the intervention (surgery) - continue with follow up visits and data collection under conservative management pathway.
2. Withdraw completely before or after surgery – no further follow up visits or data collection will occur.

There are 2 options for participants in the Conservative Management group:

1. Withdraw completely from study - no further data will be collected.
2. Cross over to surgery – continue with the follow up visits and data collection as scheduled. Participants who wish to cross over from conservative management to tonsillectomy should contact the clinical team to discuss. It is the clinician's decision whether they wish to see the participant at a clinic visit to discuss cross over or to list them for surgery following a phone call. Those who still meet the SIGN guidelines for tonsillectomy will be put forward for surgery. Participants will not have to visit their GP again to be referred.

All data collected up until withdrawal will be retained for NATTINA research purposes.

15. Data Monitoring, Quality Control and Quality Assurance

15.1 Discontinuation Rules

The internal pilot study performed at 6 out of 9 sites serves as a feasibility study and only on success of this can the full NATTINA trial go ahead. Success of the pilot will be dependent on establishing 6 screening sites who demonstrate acceptability of randomisation, with an average of 11 potential subjects screened per month per site. The target minimum recruited is 72 subjects. The process will be overseen by the DMEC and the TSC prior to consideration by HTA who will decide whether to release the full funding.

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the DMEC and/or TSC, Sponsor, regulatory authority or ethics committee concerned.

15.2 Monitoring, Quality Control and Assurance

The trial will be managed through the NCTU. The TMG will include: Prof Janet Wilson (CI), James O'Hara (Co-I), Dr Scott Wilkes (Co-I), Dr Nikki Rousseau (Health Research Methodologist), Dr Katie Haighton (Qualitative Research Lead), Dr Deborah Stocken (Deputy Director Newcastle Clinical Trials Unit), Dr Lesley Hall (Senior Trial Manager), Alexander von Wilamowitz-Moellendorff (Trial Manager), Rebecca Harrison (Trial Manager), Prof Luke Vale (Health Economist), Tara Homer (Health Economist), Tony Fouweather (Statistician) and Sally Gerrard (Project Secretary).

The Principal Investigators will be responsible for the day-to-day study conduct at site.
The NCTU will provide day-to-day support for the sites and provide training through Investigator meetings, site initiation visit and routine monitoring visits.

Quality control will be maintained through adherence to the NCTU's Standard Operating Procedures (SOPs), study protocol, the principles of GCP, research governance and clinical trial regulations.

A Trial Steering Committee will be established to provide overall supervision of the trial. The TSC will consist of Prof Janet Wilson (CI), Prof John Birchall (Independent Chair), Mrs Susan Clarke (Independent Clinician), Mr Uzair Afaq (Public Member), Mr James Kyle (Public Member), Dr Catherine Hewitt (Independent Statistician) and observer members of the TMG. The committee will meet prior to the start of the internal pilot, and then annually during recruitment and for the duration of the trial.

An independent DMC will be convened to undertake independent review and will monitor efficacy and safety endpoints. The committee will consist of Mr Andrew Swift (Independent Chairperson), Mr Tim Woolford (Independent Clinician) and Prof Robert West (Independent Statistician), and will first meet to discuss and advise on the inclusion of an interim analysis and possible adoption of a formal stopping rule for efficacy or safety. The committee will then meet at the end of the internal pilot and annually throughout the course of the trial.

The Patient and Public Involvement (PPI) Group will consist of a group of patients that meet annually with a researcher from Newcastle University to act as a research advisory group to discuss the design of NATTINA and any issues that have occurred. PPI members will also be contacted via email for more urgent matters.

15.3 Study Monitoring

Monitoring of study conduct and data collected will be performed by a combination of central review and site/remote monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by the Trial Manager. The main areas of focus will include consent, serious adverse events and essential documents in study.

Site monitoring will include:

- All original consent forms will be reviewed as part of the study file. The presence of a copy in the patient hospital notes will be confirmed for 100% of participants.
- All original consent forms will be compared against the study 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 Investigator Site Files will be checked.
- Source data verification of primary endpoint data and eligibility data for 100% of participants entered in the study.

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission.
- All documentation essential for study initiation will be reviewed prior to site authorisation.

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

The study may be subject to inspection and audit by The Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s)/institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct assess to source data/documents.

16. Safety Monitoring and Reporting

16.1 Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a study intervention or procedure has been administered which is judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a study procedure. The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship. Medical conditions/diseases present before the start of an intervention or procedure are only considered adverse events if they worsen after the start of an intervention or procedure.

16.2 Causality

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e. definitely, probably or possibly related) are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the main REC and other bodies will be informed of both points of view.

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

16.3 Unexpected Adverse Event

A related adverse event that is not listed in the study protocol as an expected occurrence in the circumstances of this trial.

16.4 Serious Adverse Event (SAE)

An untoward occurrence (whether expected or not) that:-

- Results in death
- Is life-threatening (refers to an event in which the subject was at 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)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

- Is otherwise considered medically significant by the investigator

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

16.5 Severity (Intensity) of Adverse Events and Adverse Reactions

Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, severe):

- Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
- Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

An AE may be severe but not serious.

16.6 Expected Adverse Reactions:

Most adverse events that occur in this study, whether they are serious or not, will be expected due to the interventions and study procedures of this study. Expected AEs are summarised in the table below.

Common	Uncommon	Very Rare
Post-operative pain		
Post-operative bleeding		
Temporary changes in taste/tongue sensation	Long-term changes in taste/tongue sensation	
Difficulty swallowing		
Nausea		
Vomiting		
Infection		
	Chip/knock out of tooth	
		Death

Frequencies are defined as common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

16.7 Protocol Specifications

For purposes of this protocol:

- Adverse events must be related to the study intervention.
- Adverse events will be collected and recorded at the 2 post-operative phone calls at 1 and 2 weeks after surgery.
- Any serious adverse events will be recorded throughout the duration of the trial until the 24 month follow up and once they are resolved.
- Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.
- Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

16.8 Recording and Reporting Serious Adverse Events or Reactions

All adverse events related to the study intervention should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance. A flowchart (figure 1) is given below to aid reporting procedures.

There is a very rare possibility of death in patients in either the conservative management arm or surgery arm. Any death of a trial participant that is related to surgery or a severe symptom of tonsillitis, e.g. peritonsillar abscess, should be immediately reported to the NCTU via the Trial Manager/CI once the site been made aware.

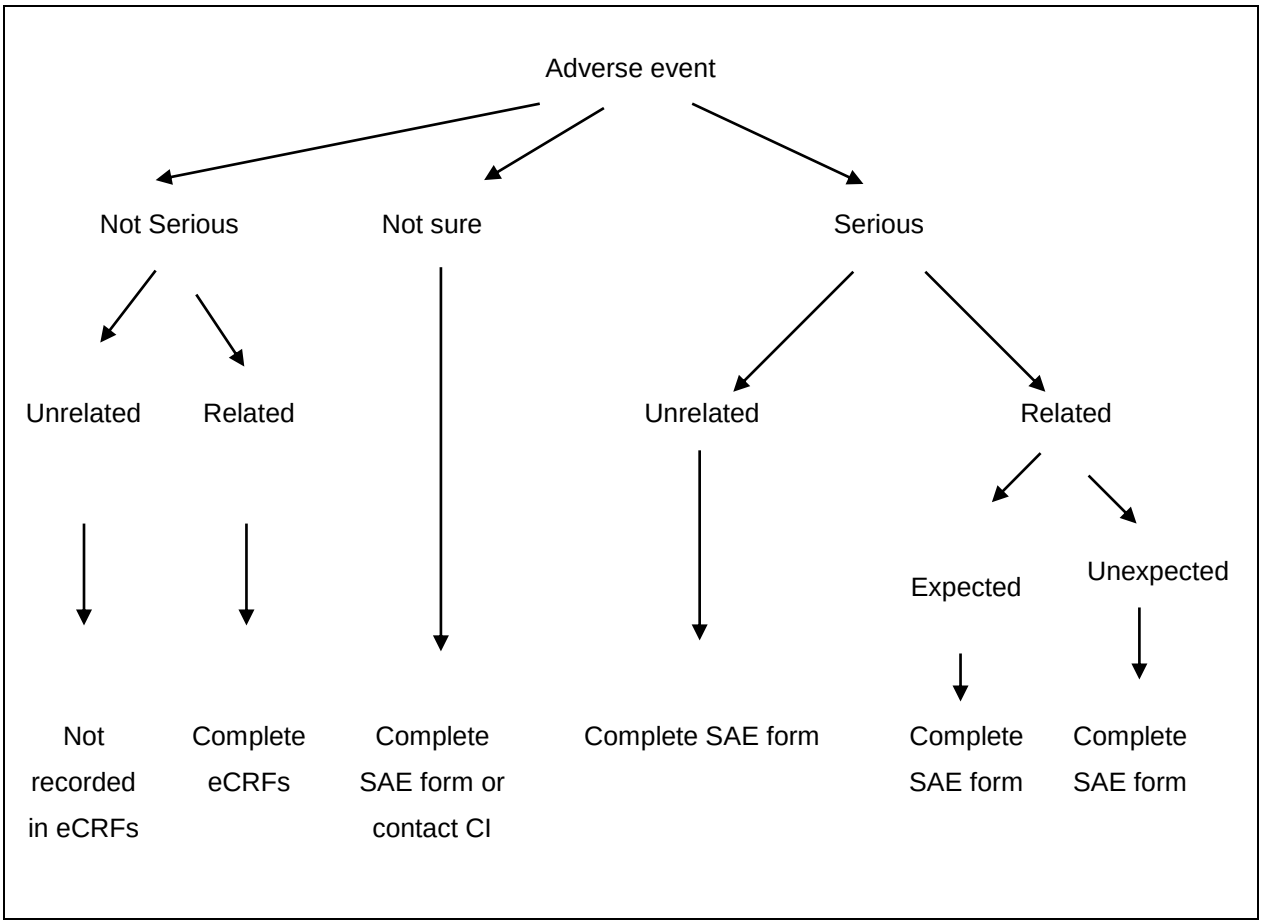
Adverse Event (AEs):

All non-serious related adverse events during study participation will be reported on the study CRF and sent to the Trial Manager within one month of the form being due. Severity of AEs will be graded on a three-point scale (mild, moderate, severe). Relation (causality) and seriousness of the AE to the treatment should be assessed by the investigator at site in the first instance. The individual investigator at each site will be responsible for managing all adverse events according to local protocols.

Serious Adverse Event (SAEs):

All SAEs during study participation shall be reported to the CI within 24 hours of the site learning of its occurrence. The initial report can be made by completing an SAE report form and sending it either by fax or email. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to study procedures should be assessed by the investigator at site, as should the expected or unexpected nature of the SAE. Local investigators should report any SAEs as required by their local R&D Office. The CI will ensure The Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor is notified of any SAEs in accordance with local trust policy. Local investigators should report any SAEs as required by their local R&D Office

Figure 1



Contact details for reporting SAEs
Please send SAE form(s) via FAO Trial Manager [**Fax: 0191 580 1106**]

17. Ethics and Regulatory Issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Favourable ethical opinion from an appropriate REC will be sought prior to commencement of the study. NHS R&D approvals will be sought at each site before recruitment can commence. The NCTU will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Participant Information sheets will be provided to all referred patients and written informed consent will be obtained prior to randomisation and any study interventions.

18. Confidentiality and Data Storage

18.1 Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, a unique participant ID will be assigned to each participant at randomisation. This participant number, along with the participant's initials and date of birth, will be used on CRFs and questionnaire front covers. eCRFs will be securely stored on MACRO with restricted access.

Participants will be made aware via the PIS, and will give consent for their name and address to be used by the NCTU to send out questionnaires. They will also consent for their email address and phone numbers to be accessed by our commercial partner Inteleme, to send out weekly alert prompts and STARs. This information will be stored on a password protected electronic database at Newcastle University. Paper forms will be securely stored in a locked cabinet with restricted access.

Participants will sign a consent form giving their permission for a researcher from Newcastle University to contact them to invite for an interview. Declining patients will only be contacted by the researcher if an expression of interest form has been returned. Otolaryngology staff who will be invited for interviews will already be involved in the study at the participating sites. GP details will be collected from public information.

Written consent will be sought from the participant to allow access to their electronic GP records for primary health care linkage data. The patient's NHS number, along with their initials and date of birth, will be used to link primary care data to the participant's ID. No personal identifiable information (other than initials and date of birth) will be transferred from the GP records onto MACRO.

Only the clinical team at the participating sites will have access to key data which links study identifiers to individual datasets.

The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

18.2 Long Term Data Storage

On closure of the study, all study documentation including Investigator Site Files, CRFs, consent forms and questionnaires, will be kept for 5 years in accordance with the sponsor's SOPs and policies.

19. Insurance and Finance

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is Sponsor and through the Sponsor, NGS indemnity is provided in respect of potential liability and negligent harm arising from

study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantative contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the. This is a non-commercial study and there are no arrangements for non-negligent compensation.

NIHR Health Technology Assessment Programme is funding the study.

Participants will receive a £25 high street gift voucher at the end of their 1st and 2nd year follow up as a gesture of thanks for participating in the study. Travel expenses will be contributed towards for the 2 NATTINA clinic visits that the patients need to attend at 12 months and 24 months.

Recruited and declining patients who consent to an in-depth interview for the qualitative process evaluation will receive a £15 high street gift voucher as a gesture of thanks.

20. Study Report and Publications

The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator.

It is planned to publish this study in peer review articles and to present data at national and international meetings with appropriative approval from the HTA. Results of the study will also be reported to the Sponsor and Funder, and will be available on their website. All manuscripts, abstracts or other modes of presentation will be reviewed by the TSC and Funder prior to submission. Individuals will not be identified from any study report.

A lay summary of the study results will be made available to the participants on the NATTINA website at the end of the study. Participants can also be informed about their contribution to the study upon request.

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22. Appendices

22.1 Appendix 1:

Extract from SIGN guidelines 117 – Management of sore throat and indications for tonsillectomy

SURGERY FOR RECURRENT TONSILLITIS

A **Watchful waiting is more appropriate than tonsillectomy for children with mild sore throats.**

A **Tonsillectomy is recommended for recurrent severe sore throat in adults.**

D **The following are recommended as indications for consideration of tonsillectomy for recurrent acute sore throat in both children and adults:**

- **sore throats are due to acute tonsillitis**
- **the episodes of sore throat are disabling and prevent normal functioning**
- **seven or more well documented, clinically significant, adequately treated sore throats in the preceding year or**
- **five or more such episodes in each of the preceding two years or**
- **three or more such episodes in each of the preceding three years.**

Cognisance should also be taken of whether the frequency of episodes is increasing or decreasing.

Evidence on exactly which children with sore throats benefit from tonsillectomy is not available, but current evidence suggests that the benefit of tonsillectomy increases with the severity and frequency of sore throats prior to tonsillectomy. Apart from adults with proven recurrent group A streptococcal pharyngitis, evidence on which adults will benefit from tonsillectomy is not available.

There are situations in which tonsillectomy may be appropriate outwith these criteria. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan.

This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available.

☑ When in doubt as to whether tonsillectomy would be beneficial, a six month period of watchful waiting is recommended prior to consideration of tonsillectomy to establish firmly the pattern of symptoms and allow the patient to consider fully the implications of an operation.

POSTOPERATIVE CARE

☑ At the time of discharge, patients/carers should be provided with written information advising them whom to contact and at what hospital unit or department to present if they have postoperative problems or complications.

D **Patients should be made aware of the potential for pain to increase for up to 6 days following tonsillectomy.**

☑ Patients/carers should be given written and oral instruction prior to discharge from hospital on the expected pain profile and the safety profile of the analgesic(s) issued with particular reference to appropriate dose and duration of use. They should be issued with enough analgesic to last for a week.

A **Routine use of anti-emetic drugs to prevent postoperative nausea and vomiting (PONV) in tonsillectomy is recommended.**

A **NSAIDs are recommended as part of postoperative analgesia to reduce PONV.**

A **A single intraoperative dose of dexamethasone** *(dose range 0.15 to 1.0 mg/kg; maximum dose range 8 to 25 mg)* **is recommended to prevent postoperative vomiting in children undergoing tonsillectomy or adenotonsillectomy.**

B **A single dose of 10 mg dexamethasone at induction of anaesthesia may be considered to prevent PONV in adults undergoing tonsillectomy or adenotonsillectomy.**

B **Stimulation of the acupuncture point P6 should be routinely considered in patients at risk of PONV where anti-emetic drug prophylaxis is not suitable.**

This Quick Reference Guide provides a summary of the main recommendations in SIGN guideline 117: **Management of sore throat and indications for tonsillectomy**.

Recommendations are graded A B C D to indicate the strength of the supporting evidence. Good practice points ☑ are provided where the guideline development group wishes to highlight specific aspects of accepted clinical practice.

Details of the evidence supporting these recommendations can be found in the full guideline, available on the SIGN website: www.sign.ac.uk

SIGN
Scottish Intercollegiate Guidelines Network
Part of NHS Quality Improvement Scotland

NHS Quality Improvement Scotland

117 Management of sore throat and indications for tonsillectomy

Quick Reference Guide

April 2010

COPIES OF ALL SIGN GUIDELINES ARE AVAILABLE ONLINE AT WWW.SIGN.AC.UK

PRESENTATION AND DIAGNOSIS IN GENERAL PRACTICE

C **Practitioners should be aware of underlying psychosocial influences in patients presenting with sore throat.**

☑ Sore throat associated with stridor or respiratory difficulty is an absolute indication for admission to hospital.

C **The Centor clinical prediction score should be used to assist the decision on whether to prescribe an antibiotic, but cannot be relied upon for a precise diagnosis.**

The Centor score gives one point each for:

- tonsillar exudate
- tender anterior cervical lymph nodes
- history of fever
- absence of cough.

The likelihood of group A beta-haemolytic streptococcus (GABHS) infection increases with increasing score, and is between 25-86% with a score of 4 and 2-23% with a score of 1, depending upon age, local prevalence and seasonal variation.

Streptococcal infection is most likely in the 5–15 year old age group and gets progressively less likely in younger or older patients. The score is not validated for use in children under three years.

D **Throat swabs should not be carried out routinely in primary care management of sore throat.**

☑ Throat swabs may be used to establish aetiology of recurrent severe episodes in adults when considering referral for tonsillectomy.

☑ If breathing difficulty is present, urgent referral to hospital is mandatory and attempts to examine the throat should be avoided.

GENERAL MANAGEMENT OF SORE THROAT

Diagnosis of a sore throat does not mean that an antibiotic has to be administered. Adequate analgesia will usually be all that is required.

ANALGESIA IN ADULTS

A **Ibuprofen 400 mg three times daily is recommended for relief of fever, headache and throat pain in adults with sore throat.**

A **In adults with sore throat who are intolerant to ibuprofen, paracetamol 1 g four times daily when required is recommended for symptom relief.**

ANALGESIA IN CHILDREN

☑ In children with sore throat, an adequate dose of paracetamol should be used as first line treatment for pain relief.

A **Ibuprofen can be used as an alternative to paracetamol in children.**

D **Ibuprofen should not be given routinely to children with or at risk of dehydration.**

ADJUNCTIVE THERAPIES

B **Echinacea purpurea is not recommended for treatment of sore throat.**

No good quality evidence on the effectiveness of non-prescription throat sprays, lozenges and gargles was identified.

Evidence on corticosteroids for pharyngitis is conflicting and no recommendation is made.

In patients with acute glandular fever (infectious mononucleosis) requiring hospitalisation, corticosteroids may have a role when pain and swelling threaten the airway or where there is very severe dysphagia.

ANTIBIOTICS IN ACUTE AND RECURRENT SORE THROAT

A **Antibiotics should not be used to secure symptomatic relief in sore throat.**

☑ Antibiotic prophylaxis for recurrent sore throat is not recommended.

☑ In view of increases in healthcare-acquired infections and antibiotic resistance in the community, unnecessary prescribing of antibiotics for minor self limiting illness should be avoided.

☑ In severe cases, where the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld. (Penicillin V 500 mg four times daily for 10 days is the dosage used in the majority of studies. A macrolide can be considered as an alternative first line treatment, in line with local guidance.)

☑ In certain unusual circumstances, such as epidemics, more widespread prescription of antibiotics may be recommended and the relevant public health guidance should be followed.

☑ Ampicillin-based antibiotics, including co-amoxiclav, should not be used for sore throat because these antibiotics may cause a rash when used in the presence of glandular fever.

C **Sore throat should not be treated with antibiotics specifically to prevent the development of rheumatic fever and acute glomerulonephritis.**

C **Antibiotics may prevent cross infection with GABHS in closed institutions (such as barracks, boarding schools) but should not be used routinely to prevent cross infection in the general community.**