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# North of England and Scotland Study of Tonsillectomy and Adeno-tonsillectomy in Children (NESSTAC)

## Protocol Version 5 dated 22 November 2007

(incorporating amendment 1, 2, 3 & 4)

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| **Funder**: | HTA Ref: 99/20/03 |
| **Sponsor**: | Newcastle upon Tyne Hospitals NHS Foundation Trust |
| **Monitor**: | Trial Steering Committee. (The trial does not have a data monitoring committee since it examines routine therapies) |


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# Protocol Signatures

## Protocol authorisation signatories

Signature Date 22nd November 2007

Professor Janet Wilson, Principal Clinical Investigator

Signature Date 22nd November 2007

Professor John Bond, Lead Investigator

## Investigator signature

I confirm that I have read and understood protocol version 5 dated 22nd November 2007. I agree to comply with the study protocol, the principles of GCP and the appropriate reporting requirements.

Signature …… Date ……

Print Name ……

Site Name/I.D……

# Contents

List of abbreviations and definitions

| Abbreviation | Definition |
|---|---|
| A&E | Accident and Emergency |
| CCA | Cost Consequences Analysis |
| CEA | Cost Effectiveness Analysis |
| CHSR | Centre for Health Services Research |
| CUA | Cost Utility Analysis |
| ENT | Ear, Nose and Throat |
| GP | General Practitioner |
| LREC | Local Research Ethics Committee |
| MREC | Multi-centre Research Ethics Committee |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NHS | National Health Service |
| nvCJD | New variant Creutzfeldt-Jakob Disease |
| UK | United Kingdon |
| USA | United States of America |

# Summary


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|---|---|
| **Title**: | North of England and Scotland Study of Tonsillectomy and Adeno-tonsillectomy in Children (NESSTAC) |
| **Protocol version**: | 5 |
| **Protocol date**: | 22nd November 2007 |
| **Principal Investigators**: | Professor Janet Wilson and Professor John Bond |
| **Sponsor**: | Newcastle upon Tyne Hospitals NHS Foundation Trust |
| **Funder**: | HTA Ref: 99/20/03 |
| **Aim and rationale for trial**: | To evaluate the cost-effectiveness of tonsillectomy/adeno-tonsillectomy in children with recurrent throat infections in comparison with standard non-surgical management in children aged under 16 with recurrent throat infections. |
| **Study design**: | A simple prospective pragmatic randomised controlled trial with economic analysis and prospective cohort study of non-trial participants comparing surgical intervention with conventional medical treatment. |
| **Interventions**: | The treatment arm will receive tonsillectomy and adeno-tonsillectomy while in the control arm non-surgical conventional medical treatment only will be used. |
| **Primary objective**: | To evaluate if tonsillectomy/adeno-tonsillectomy reduces the number of episodes of sore throats among children to a clinically significant extent. |
| **Primary outcome**: | Reported number of episodes of sore throat over two years |
| **Secondary outcomes**: | Reported number of episodes of sore throat, otitis media and upper respiratory tract infection which invoke a GP consultation; reported number of symptom-free days; reported severity of sore throats and surgical and anaesthetic morbidity. |
| **Study sites**: | 5 Hospitals in the UK |
| **Study population**: | The trial population will be 406 children aged 4-15 on their last birthday with recurrent sore throat referred by primary care to the 5 otolaryngology departments |
| **Study duration**: | 7 years ( July 2001- July 2008) |

# 1 Background

Sore throats result in a loss of at least 35 million school or work days annually in the UK, mostly in winter/early spring[1]. The cost of GP consultations for sore throat alone has been estimated at £60m. Even more than this is spent by the NHS annually on 90,000 tonsillectomy procedures, approximately half of which are in children. 70 – 80% are for recurrent sore throats, with most of the remainder being performed for obstructive symptoms[2;3]. The incidence of tonsillectomy has risen since the early 1990's, although levels are still much lower than in the 1930's, when 100,000 operations were performed in UK school children[4]. Adenoidectomy is performed with tonsillectomy in about one third of patients. Private medical insurance is associated with higher selective ENT surgical rates under the age of 7 years[5] and 16% of UK ENT activity is in the independent sector. Therefore figures based purely on NHS returns inevitably underestimate the total activity. In addition to the health care costs, tonsillectomy incurs parental costs as one parent usually resides in hospital overnight. Thereafter the average time to return to normal activity for under 15 year olds is 12 days[6].

## 1.1 Current practice

There is a broad similarity in the criteria for tonsillectomy in clinical guidelines in the UK[7;8] and North America[9]. The minimum criteria are typically a 2-year history of 3 (USA) to 4 (UK) sore throats of moderate severity (5 day duration) per annum. This is despite evidence that even histories that 'seem impressive' may not be confirmed on close scrutiny in the majority[10]. The complex psychosocial influences on tonsillectomy rates include parental enthusiasm for intervention[11], lack of information[12] and maternal use of psychotropic drugs which increases two-fold the rate of consultation for childhood sore throat[13;14]. Guidelines may not be uniformly implemented, even when locally derived. Surgeons tend to break guidelines more often in favour of performing than withholding surgery[7].

National and international variations in the rates of adeno-tonsillectomy have been recognised for decades. Even in the 1930's, 50% of UK and USA children received a tonsillectomy, while the rate was 0.5% or lower in Germany[4]. A recent survey of such variation in Quebec, highlighted the importance of clinical uncertainty among physicians about the recommendation of surgical intervention[15], providing further support for primary research. The Scottish National Tonsil Audit showed that rates of tonsillectomy in childhood varied from <4/10,000 in Forth Valley to almost 10/10,000 in Dumfries and Galloway[2].

Differential costs and benefits of surgery at different age groups are not known**.** The tonsils are traditionally thought to undergo a period of 'physiological enlargement' around school entry. At this time also, pathological sequelae may include otitis media. Older children and adolescents, may have a somewhat different natural history, and illness at this age has rather different (educational) implications.

## 1.2 Complications and psychological impact of tonsillectomy

Mortality from tonsillectomy has been estimated at 1/16000 to 1/35000[16], but surgical risk at this level is hard to measure, to conceptualise and to convey. The major nonfatal complications are infection, haemorrhage (2.15%), and pain which lasts on average 5 to 6 days[17;18] and may be inadequately treated in children[19]. Haemorrhage is unpleasant, requires intravenous fluid administration, with or without blood transfusion and return to theatre. The reported rate of second anaesthetic for haemostasis varies widely from 0.75% in one British review[6], to as low as 0.06% in a study of almost 9409 children in Toronto[20]. The post tonsillectomy readmission rate is up to 7%[6], but in Newcastle in childhood only 2.3% (unpublished data; Department of Clinical Effectiveness, Freeman Hospital, Newcastle). The overall reported complication rate ranges from 8%[2] to 14%[18], the majority being relatively minor - sore throat, nausea, fever, dysphagia.

Most 2 to 10 year olds undergoing ENT surgery show behavioural changes such as attention seeking, temper tantrums and night waking and there is also anecdotal evidence for depression after tonsillectomy[21]. Younger children, due to cognitive immaturity seem less well able to adapt to hospitalisation[22;23].

Late sequelae may include lower postoperative serum immunoglobulin levels but these have been ascribed to reduction in antigen stimulation[24]. There is continuing debate[25], about the suggestion that tonsillectomy increases the risk of Hodgkin's lymphoma. A substantial Scandinavian population based cohort study found an increased risk of Hodgkin's disease, especially in younger children[26]. The risk of transmission of nvCJD from contaminated tonsillectomy instruments remains quite unquantified. Some centres are costing the use of disposable tonsillectomy sets.

### 1.3 Clinical effectiveness of tonsillectomy

Despite the frequency of tonsil dissection, there is a remarkable lack of robust evidence for its efficacy. Uncontrolled patient reports suggest the procedure to be very effective but recurrent sore throat, particularly in childhood may be a self limiting disease. Where non-intervention control groups have been studied, the benefits of tonsillectomy seem almost to disappear after two years. Available studies are either 20 to 30 years old or confined to small numbers of severely affected individuals with limited general applicability. The recently published Cochrane review concludes that there is no evidence from randomised controlled trials to guide the clinicians in formulating the indications for surgery in children or adults[27]. The authors state the need for high quality evidence from randomised controlled trials to establish its effectiveness and that these should assess the effectiveness of the procedure in patients with throat infections of differing severity and frequency.

The Scottish National Tonsillectomy Audit[2] showed high levels of patient satisfaction and that 80% of subjects did not consult a doctor in the subsequent 12 months. However, over the past 30 years a number of controlled studies with longer follow-up indicate marginal and diminishing levels of clinical benefit over a period of non-intervention. There are no substantial claims for the benefit of childhood tonsillectomy after 2 years. Roos[28] assessed the benefit to be 1 to 1.5 fewer sore throats (0.5 to 1 episode per annum) over the first 2 years after surgery in those with 3 to 4 episodes per annum preoperatively. Other studies[29-31] showed benefits of the order of ~1.5 fewer sore throats versus controls in the first postoperative year and on average single fewer episode in the second year. All of these and other available studies provide inadequate evidence because of poor definition of entry and outcome criteria, failure to include intention to treat calculations and small or skewed samples[32]. Even the only scientifically acceptable study by Paradise and colleagues[18] suffered from comparatively small numbers of a skewed population of more severely affected children. The benefits of surgery were more marked (approximately 1.75 fewer episodes in year 1, 1.5 in year 2) but equally short lived. The drop out rate was 34% by the end of year 2 and 1 in 3 of the control group underwent surgery and were excluded from analysis. Also, the very active therapy of the control arm may have mitigated any impact of surgery. The Paradise group went on to study a more typical i.e. less severely affected group of children, but the full results of this study, near completion in 1992 have never been reported. Weight gain is a cited supplementary benefit of tonsillectomy. Two recent studies showed accelerated weight gain postoperatively, but as the children were shown to be of normal or above average height and weight preoperatively, this effect may be undesirable[33]. There appears so far to be only minimal additional benefit from adenoidectomy or adenotonsillectomy in recurrent acute otitis media [17].

A straw poll, for this protocol, of consultant otolaryngologists asked: what level of reduction in sore throat would justify removal of the tonsils? Replies were remarkably consistent - at least 2 sore throats fewer per annum. No published trial to date shows a benefit of this magnitude, even in the first year after surgery. There is a pressing need for a UK, pragmatic trial to evaluate the cost-effectiveness of childhood tonsillectomy.

## 2 Objectives and purpose

### 2.1 Purpose

To answer the key research question "What is the cost-effectiveness of tonsillectomy/adeno-tonsillectomy in children with recurrent throat infections?" in comparison with standard non-surgical management in children aged under 16 with recurrent throat infections. Assessment of

outcome will emphasise those which are important to children themselves and their parents or carers.

### 2.2 Objectives

- Does tonsillectomy/adeno-tonsillectomy reduce the number of episodes of recurrent sore throats among children to a clinically significant extent?
- Are there differences in clinical outcome for the age groups: 4-7, 8-11, 12-15 years?
- What is the cost effectiveness of tonsillectomy/adeno-tonsillectomy among children and what are the costs and benefits to families?
- What are the important outcomes of tonsillectomy/adeno-tonsillectomy for children and their parents/carers and what is the importance of these to children and their parents' quality of life?
- What are parents' (and older children's) preferences for different treatment options for recurrent sore throat?
- How representative of the target population are trial participants?

## 3 Study design

### 3.1 Trial design

A simple prospective pragmatic randomised controlled trial with economic analysis comparing surgical intervention with conventional medical treatment.

### 3.2 Cohort study design

We anticipate that a large majority of participants who decline randomisation to the trial will opt for, and receive, surgery. Therefore, in order to assess the external validity of the trial results, we will recruit a cohort of children receiving surgery, randomly selected from those who decline to participate in the trial. Base-line characteristics will be collected for all who decline randomisation and a random sample of children receiving surgery will be followed up for 24 months. In addition a sample of older children and their carers from the Newcastle cohort will be invited to take part in an interview to measure their preferences and utilities.

### 3.3 Interventions

The treatment arm will receive tonsillectomy and adeno-tonsillectomy while in the control arm non-surgical conventional medical treatment only will be used.

### 3.4 Outcome measurement

The primary clinical outcome is the reported number of episodes of sore throat in the two years after randomisation.

Secondary clinical outcomes include reported number of episodes of sore throat, otitis media and upper respiratory tract infection which invoke a GP consultation; reported number of symptom-free days; reported severity of sore throats and surgical and anaesthetic morbidity. In addition to the measurement of these clinical outcomes, the impact of the treatment on costs and quality of life will be assessed. There will also be an economic evaluation.

## 4 Subject selection

### 4.1 Setting

Inpatient facilities and outpatient clinics of 5 hospitals in the North of England and Scotland: Freeman Hospital, Newcastle upon Tyne; Alder Hey Children's Hospital, Liverpool; Booth Hall Children's Hospital, Manchester; Yorkhill Royal Hospital for Sick Children, Glasgow; and Bradford Royal Infirmary and general practices with which study participants are registered. Freeman Hospital, Newcastle is a large teaching hospital with a mixed adult and paediatric ENT unit. The Unit has a wide urban and rural catchment area including Newcastle and Gateshead, Northumberland and north west Durham. Alder Hey Hospital, Liverpool and Booth Hall Hospital, Manchester house two of the largest paediatric ENT units in the UK covering catchment areas

in and around Liverpool and Manchester. Yorkhill is a busy university hospital with the largest children's ENT Unit in Scotland and Bradford Royal Infirmary is one of the major hospitals within west yorkshire. It has recently obtained teaching hospital status with the opening of its medical school. The ENT unit acts as a hub and supports clinics in Airedale and Dewsbury. The unit supports the majority of adult and paediatric care.

## 4.2 Target population

The trial population will be children aged 4-15 on their last birthday with recurrent sore throat referred by primary care to 5 otolaryngology departments in Newcastle, Liverpool, Manchester, Glasgow and Bradford. In 1999 a total of 2683 tonsillectomy/adeno-tonsillectomy procedures were done for children in four of these centres: Liverpool (750), Manchester (440), Newcastle (545), Glasgow (498) and Bradford (450) of which some two-thirds will be referrals for recurrent sore throat.

### 4.2.1 Inclusion criteria

The study will use entry criteria drawn from the Northern regional guidelines[7]. Children (or carers) reporting experience of 4 or more episodes of sore throat within each of 2 years or 6 or more episodes of sore throat within 1 year will be eligible. We have considered pre-randomisation prospective data recording to operationalise stricter inclusion criteria for severity, but have rejected these as our aim is to operationalise current UK clinical practice.

### 4.2.2 Exclusion criteria

Children will be excluded if they require hospitalisation due to quinsy; have obstructive symptoms suggestive of clinically significant sleep apnoea syndrome, have rare medical conditions such as glomerulonephritis or Henoch Schonlein purpura; have previously had a tonsillectomy; have suspected velopharyngeal insufficiency, have co-morbidity that means they are unable to undergo the operation within the next 6 months, have a bleeding disorder, or have congenital/valvular heart disease.

## 4.3 Number of subjects required

We estimate a completed sample size at follow up of 284 children. Allowing for an attrition rate of around 30% we will need to recruit a total of 406 children to the trial to achieve the estimated sample of 284 (who will complete the trial). Within the study hospitals some 1700 tonsillectomies/adeno-tonsillectomies are currently performed annually. Only two thirds of these will have recurrent sore throats. In any trial where the intervention is widely used in current practice there are likely to be large numbers of eligible participants who opt for the intervention treatment and decline participation in the trial. We estimate that this could be up to one half of all eligible referrals from primary care. The maximum available for randomisation is therefore estimated as 566 per annum. Loss of eligible subjects in the trial is expected due to holiday periods and ‘winter pressures’. On the experience of loss in other trials (50%) a conservative estimate would be 283 per annum. If we assume a conservative rate of attrition of 30% over two years we would expect 198 completing trial participants to be recruited in a 12 month period. Given seasonal effects a full 2 years would be necessary to recruit the estimated sample size.

The cohort sample will be identified from participants who indicated a preference not to be randomised within the trial and who agreed to data collection. An appropriate sampling fraction will be used once non-participation in the trial can be estimated.

# 5 Subject recruitment

Recruitment to the study will take place in secondary care. All GP referrals to study centres of children with recurrent sore throat will be considered by participating surgeons. Arrangements are in place in each centre for eligible children to be referred to the clinical applicants. GPs will be informed of this reorganisation. This will facilitate efficient use of outpatients clinics at which trial participants would be recruited.

Trained Research Nurses will introduce the trial to patients who will be shown a video regarding the main aspects of the trial. Patients will also received information sheets. Research Nurses will discuss the trial with patients in light of the information provided in the video and information sheets. Patients will then be able to have an informed discussion with the participating consultant. Research Nurses will obtain written consent from patients willing to participate in the trial. Information sheets and consent forms are provided for all parents involved in the trial however these have been amended accordingly in order to provide separate information sheets and consent form which are suitable for children and teenagers. All information sheets, consent forms and the video transcript have been translated into Bengali, Punjabi, Gujarati, and Urdu. There are also separate information sheets and consent forms for the cohort group

# 6 Interventions

## 6.1 Treatment

Tonsillectomy and adeno-tonsillectomy with adenoid curettage and tonsillectomy by dissection or bipolar diathermy. Most (80%) UK surgeons use the conventional dissection method[6] and the remainder use bipolar diathermy. Both methods will be allowed in the trial according to surgical preference. Surgical intervention will take place within four weeks of randomisation.

## 6.2 Control

Non-surgical conventional medical treatment only will be used. There will be no active intervention protocol since no single prescribing strategy would be able to cover all patients[34]. The referring GP will be free to treat as in their current practice. The use of usual treatment rather than an active intervention protocol is considered important for the implementation of study findings since 'surgical enthusiasts' may argue against the findings were the control group to be atypically and over rigorously treated

# 7 Randomisation

Independent world wide web based computer randomisation will allocate participants to treatment arms. Randomisation will take place once informed consent to the study has been completed and base-line data collected. The sample will be stratified by age of child at last birthday. Blocked randomisation will be used to ensure that within each centre, within each of the three age groups (4-7, 8-11, 12-15) children will be allocated in equal numbers to each arm of the trial. Where trial sites are unable to access the world wide web they will telephone the coordinating centre (University of Newcastle) in order for web based randomisation to be completed on their behalf.

Sampling for the cohort study will similarly be stratified by age.

# 8 Blinding

Health technology assessment is essentially a pragmatic activity conducted in normal clinical practice, rather than an exploratory activity conducted in highly controlled settings. It follows that blinding doctors and patients to treatment is not desirable since it distorts normal clinical practice. Nor is it practicable. In contrast, blinding assessors is important because it minimises subjective bias towards a given treatment. All research staff conducting interviews or processing postal questionnaires and diaries will be blind to treatment modalities of all participants. This will be facilitated by separating the responsibility for recruitment and randomisation from outcome assessment. Furthermore, participants will be encouraged to respond to questions without describing their treatment regime. In this way, we will minimise subjective bias towards a given treatment.

# 9 Data

## 9.1 Data to be collected

All participants will be followed-up for 24 months from the date of initial randomisation. To minimise recall bias, data on sore throats will be gathered by a simple, structured daily health diary completed and returned by participants on a monthly basis for 24 months. Experience of similar studies suggests that with appropriate telephone reminders 90% of diaries will be returned completed.

In addition simple outcome questionnaires will be administered to trial and cohort study participants. Overall we anticipate an 80% response rate. Interview surveys will be done at 3, 12 and 24 months after randomisation. A baseline questionnaire will be completed by all participants upon recruitment to the trial. The greater frequency of data collection in the first 12 months is necessary in order to capture data on expected changes in direct and social costs to participants in the first 12 months. Experience also suggests that data on consultation rates and prescribed medication can be gathered most accurately and reliably from medical records. Manual abstraction will be performed by trained research nurses at the end of follow up for all participants

**Table 1 Clinical outcome measures for trial and cohort studies**

| **Primary clinical outcome** | **Measurement method** | **When** | **Where** |
|---|---|---|---|
| Number of events of recurrent sore throat | Self-completed diary (by parent or child) | Daily recording but collected four-weekly for 24 months | Participants' homes |
| **Secondary clinical outcomes** | **Measurement method** | **When** | **Where** |
| Number of events of recurrent sore throat, otitis media or URTI recorded by GPs | GP records | End of 24 month follow-up period | General practices (GP records) |
| Adverse events: re-referral for tonsillectomy; number of symptom-free days | Self-completed diary (by parent or child) and GP records | Daily recording but collected four-weekly for 24 months and end of 24 month follow-up period | Participants' homes (diary) and general practices (GP records) |

**Table 2 Measuring treatment impact**

| **Impact** | **Measure** | **When** | **Where** |
|---|---|---|---|
| Costs to participants of the condition and its management | Questionnaire to children and parents | Base-line, 3, 12 and 24 months | Participant's home |
| Social costs: e.g. time off school and parental time off work | Self-completed diary (by parent or child) | Base-line, 3, 12 and 24 months | Participant's home |
| Consultation rates and prescriptions | GP records | End of 24 month follow-up period | General practices |
| Consumer satisfaction | Questionnaire to children and parents | Base-line, 3, 12 and 24 months | Participant's home |
| Health-related quality of life | PedsQL[35] questionnaire to children and parents | Base-line, 3, 12 and 24 months | Participant's home |

### 9.1.1 Economic evaluation

The cohort sample will not be included in the economic evaluation except for the purpose of validation and estimating the representativeness of cost and benefit data for trial participants.

#### *9.1.1.1 Perspective of the study*

The economic evaluation will address the study question from a societal perspective with a focus on health service and families[36].

#### *9.1.1.2 Measure of benefits used and study type*

Cost consequences analysis (CCA), cost-effectiveness analysis (CEA) and cost utility analysis (CUA) will be conducted. In CCA, all the outcomes used in the clinical study will be adopted as measures of benefits, including the QoL dimensions. In CEA, the benefits will be measured by the number of events of recurrent sore throat and the number of symptom-free days. In CUA, different health outcomes will be combined with QoL dimensions.

#### *9.1.1.3 Resources data collected within the trial and costing methods*

Medical resource data will relate to the interventions under investigation, any use of health care services due to 'sore throat' episodes not averted, treatment of drug side-effects, surgery complications and long term sequelae. Services to be monitored include: outpatient visits and hospitalisations, investigations, A&E admissions, visits and telephone consultations to and from the GP and any other health care professionals, use of medications (including antibiotics, analgesics, and drugs to manage antibiotic side-effects), and any other use of health care services in both the private and public sectors. Manpower data will be collected separately for each main category of staff. Participants' out of pocket expenses such as over the counter medicines will be reported.

Costing of health care resources will be undertaken in a parallel study and a mixed approach using micro-costing and gross-costing methods will be used[37]. We will cost resources using health service pay and price data. Where appropriate, these will be integrated using national published data[38] [39] [40]. Where relevant, costs will be broken down into capital, staff, consumable and overhead costs. This will aid the production of different cost scenarios.

The impact of the interventions on the time 'invested' by children and carers because of illness, treatment and rehabilitation will also be assessed. Children's days of restricted activity and their level of functioning; time off school; carers' time off work; children's and carers' time involved in outpatients attendance (such as travel time, waiting time and the duration of the clinical visit) and impact on children's and carers' quality of life will be monitored. For carers' in paid/unpaid work, time will be valued in monetary terms. Costing will be undertaken using the human capital approach and the friction cost method[41]. Those resources for which we find a statistically significant difference between the groups will be costed. Those which show no statistically significant difference but are of practical significance in their contribution to costs, will also be costed.

The cost analysis will not differ across the different types of economic evaluations. However in the CUA, when carers' preferences will be assessed, particular caution will be used to avoid double counting the loss of income due to work absences [42].

Whenever applicable, a discount rate of 6% will be used, which is the rate currently used by the public sector in the UK. Costs will be expressed in UK pounds sterling. Costs will be expressed in the prices of the year in which the final analysis will be carried out and if necessary inflation method will be used to update costs data.

#### *9.1.1.4 Resources/costs data collected outwith the trial*

The study is not powered to detect significant differences for rare events. Given the relatively low incidence of surgical complications, long-term sequelae due to surgery and drugs side-effects, data on the related use of resources, costs to the carers and impact on children will be gathered outwith the trial, from the literature and from experts' opinions. 'Consensus' estimates will be obtained by interviewing a panel of experts, including members of the study team and others. The source of the data will always be explicitly stated.

#### *9.1.1.5 Synthesis of costs and benefits*

Depending on the outcome measure, if there is no statistically significant evidence that one treatment strategy is more effective than another, a cost-minimisation framework will be used and the less expensive form of care will be recommended. If one strategy appears to be dominant (i.e. to be more effective and less costly than the alternative), the uptake will be

recommended. If one form of care appears to be more effective and more expensive than the comparator, estimates of incremental cost-effectiveness (and cost-utility) ratios will be generated. A judgement will be required in a policy making context to establish whether the additional benefits should be achieved sustaining the additional costs. In any case, recommendations will be made taking into account the generalisability of the results.

#### *9.1.1.6 Sensitivity analysis*

To handle uncertainty not related to sampling variations and to enhance the generalisability of the results, one-way; multi-way and extreme scenario analysis will be undertaken as appropriate and confidence intervals for cost-effectiveness ratios will be estimated under different scenarios [43]. A sensitivity analysis taking into account differences in resource use which are practically significant (i.e. potentially costly) but which have not been shown to be statistically significant, will also be undertaken. The sensitivity analysis will also make explicit all the simplifying assumptions made to collect the data[44].

The application of discounting to the benefits will also be tested in the sensitivity analysis, as well as a range of discount rates. Particular attention will also be given to whether the costs data used reflect the true marginal opportunity costs of the resources used. When more than one reliable source of information is available, such data will be used as a term of comparison. The use of different costing methods for multi-centre studies will be explored.

Earlier studies[28-31]suggest that longer term outcomes such as reduction in recurrent sore throat may show only marginal benefits. An equivalence trial with a substantially larger sample size would be necessary to capture significant longer-term outcomes. To contain the cost of the trial we have not proposed a three year follow up. However, the future sequence of clinical events and economic impact will be modelled beyond 2-year follow-up. The relevant data will be derived from studies which will be available and experts' opinions.

### 9.1.2 Measuring participants' preferences and utilities

There is a need to value the effectiveness of interventions taking account of the risk of surgery and its long-term sequelae (e.g. sleep, eating, speech, disturbances, regressive behaviour[45]). The utility assessments will also provide insight into informed choice models[46].

Older children's and carers' values will be used to elicit preferences for trade-off between the perceived risks and benefits of surgery versus drugs treatment. Preferences will relate to temporary and chronic scenarios associated with morbidity and QoL because of symptoms and treatment complications. The scenarios will be developed selecting the health outcomes and QoL domains relevant to the problem. Interviews will be carried out with a sample of older children and carers from 2 of the otolaryngology departments (Newcastle and Glasgow) and the Standard Gamble method[47] will be used to derive utilities. See Appendix 2.

## 9.2 Data handling and record keeping

Only anonymised non-identifiable data will be recorded by the site's research teams from personal medical records. Health diaries and follow-up questionnaires will be anonymous and returned to the trial centre in reply-paid envelopes. For linking purposes these data sets will have unique study identifiers. Only the lead researcher, trial manager and trial administrator will have access to the key which links study identifiers to individual data sets. Personal details (participants full name and address) will be stored on a secure database at CHSR for the prupose of sending out questionnaires and diaries centrally. All data held for analysis will be held in accordance with the Data Protection Act. On completion of the study and associated dissemination the Trial Master File will be archived in the CHSR for 10 years. Trial sites will be responsible for archiving their own documentation.

# 10 Statistical considerations

## 10.1 Sample size calculation

In this trial we anticipate a fairly large difference in the primary clinical outcome (the reported number of episodes of sore throat in the two years after randomisation) with an effect size of around 1.0, but a smaller difference in a number of psycho-social outcomes including health-

related quality of life, with an effect size of 0.33. No standard sample size formula is available for economic evaluations, and a number of methods have been proposed [48-50]. The information which is currently available limit the use of such methods in practical applications. Published data[18] suggest that tonsillectomy may lead to a reduction of approximately 1.5 days per year in missed schooling. Given a reported standard deviation of 4.5, to detect this difference with 80% power we would need approximately 142 children in each arm of the trial assuming a significance level of 5%. A sample size of 142 children in the cohort group will allow us to detect similar differences between the cohort group and propositi.

The sample will be stratified by age. With a total of 284 children, we will have approximately 47 randomised to each treatment arm in each strata. Given that the standard deviation of the number of sore throats per year is estimated at approximately 2.0[18], we will be able to estimate the difference between treatments in each strata with a standard error of 0.41. (Equivalently we would have 90% power to detect a difference of 1.35 episodes of sore throat per year in each strata assuming a type 1 error of 0.05).

It is anticipated that the difference in outcome between the two arms of the trial will be approximately 2 episodes in the second year of follow up. A sample size of 142 children in each arm should enable us to measure this difference with sufficient precision to undertake a meaningful economic analysis.

## 10.2 Statistical analysis

### 10.2.1 Main analysis

An intention to treat analysis will be performed. In particular, children randomised to non-surgical conventional medical treatment will be retained in that group for the analysis even if they subsequently receive a tonsillectomy.

The primary clinical outcome measure will be the number of episodes of sore throat. This variable will be analysed using generalised linear modelling assuming a Poisson error structure with a log link function[51]. By fitting the difference between the two experimental groups as a fixed effect, interval estimates of the effect of tonsillectomy (in each of the first two years of follow up) will be generated. These estimates will then be used in the economic analysis.

The same approach will be used to analyse the other outcomes. A Poisson error structure will be assumed for data in the form or a count (such as the number of episodes of absence from school) and normal error structure adopted for continuous variables (such as the quality of life indices).

### 10.2.2 Secondary analysis

The aim of secondary analysis is to determine whether we can identify groups of children who benefit from surgical treatment. It is hypothesised that disease severity may be an important factor. A severity index based on history of the condition during the year before entry to the study will be derived using data recorded in GP records. The relationship between severity and the effect of tonsillectomy will then be investigated using the modelling approach described above.

### 10.2.3 Economic analysis

We expect skewness in the distribution of use of resources/costs [52]. In the presence of skewness, the logarithmic transformation of data is not recommended, and the application of non-parametric tests can provide misleading results (economic studies aim to base the analysis on arithmetic means and not median values)[53;54]. The non-parametric bootstrap test can be the most appropriate[54], since it does not require any assumptions about the normality of data and equality of the variance or shape of the distributions. The t-test can be safely used if the sample size is not too small[53]. Depending on the level of skewness of data obtained we will make a judgement on which of these two methods can be safely applied. The mean costs estimates and (incremental) cost-effectiveness ratios, and conventional measures of variances will be reported[43].

### 10.2.4 Cohort analysis

The cohort of patients who decline to be randomised will be used to assess the external validity of the main study. Baseline characteristics of the cohort will be compared with those of the

study population using standard tests for the comparison of two independent samples (e.g. the t-test or Mann-Whitney test as appropriate). Outcome for the cohort will be compared with outcome for the two groups of study participants using the modelling approach described above.

# 11 Compliance and withdrawal

## 11.1 Subject compliance

Participants randomised to surgery will be followed up by research nurses to ensure compliance. Surgery will take place within 4 weeks of randomisation. Telephone reminders from research nurses will be used to encourage participants to return study diaries while both telephone from the trial manager and postal reminders will be used to encourage participants to return study questionnaires.

## 11.2 Withdrawal of participants

Any participants wishing to withdraw from the study may do so at any time.

# 12 Interim analysis and data monitoring

## 12.1 Stopping of trial

Clinical trials frequently fail to achieve the optimistic sample size predicted in study protocols. We have made conservative estimates of recruitment in this study. It is therefore likely that we will achieve sample size faster than estimated. We will identify with the Programme Manager agreed criteria for the shortening or premature stopping of the trial in the event that recruitment to the trial is quicker than estimated or falls below 60% in the second and third quarters of recruitment in each area. In the event of a site failing to achieve an agreed minimum recruitment within six months, it will be closed down and an additional centre(s) recruited.

## 12.2 Monitoring, quality control and assurance

The study has a Trial Steering Committee which meets 6 monthly and consists of Professor John Birchall, External Member, Professor John Bond, Principal Investigator, Emeritus Professor George Browning, External Member, Mr Sean Carrie, Consultant, Mr Ray Clarke, Consultant, Professor Martin Eccles, Investigator, Ms Bev Henderson, Research Nurse, Mr Haytham Kubba, Consultant, Dr Katie Lock, Trial Manager, Professor John Matthews, Independant Statistician, Ms Kath Newham, Research Nurse, Mr Chris Raine, Consultant, Ms Jane Sim, Research Nurse, Dr Nick Steen, Statistician, Ms Carole Tyson, Research Nurse, Mr Luke Vale, External Member, Professor Janet Wilson, Principal Clinical Investigator, Ms Cheryl Wiscombe, Trial Administrator, and Mr Andrew Zarod, Consultant. The Trial Steering Committee is responsible for monitoring public interest and ensuring issues relating to research governance are met.

The trial does not have a data monitoring committee since it examines routine therapies.

The Principle Investigators will be responsible for the day-to-day study conduct at site. The Trial Manager will provided day-to-day support for the sites and provide training through Principle Investigator meetings and site initiation visit.

The Trial Manager will ensure that the study in conducted in accordance with GCP through a combination of central monitoring and site monitoring visits.

Consumer involvement will be encouraged and facilitated throughout the study by the establishment of a consumer advisory panel. We will use the advisory panel to help clarify important outcomes for children and their parents (or carers) and to assist in the development of participant-oriented data-collection methods. By consumer we include here children and their parents as well as representatives of appropriate advocacy groups such as the Patients Association. Our experience of consumer panels in the development and implementation of other studies (e.g. quality of life of people with dementia and treatment for primary biliary cirrhosis of the liver) have highlighted the different types of involvement and the different ways that consumers can be involved in primary research. Parents and children will be involved in an

advisory capacity rather than in a full participatory role. We will establish and convene regularly the consumer advisory panel in which the group process will use focus group methods. Throughout the project (at least annually) we will use the advisory panel to voice participants' concerns and to identify participant-oriented solutions to such concerns.

### 12.3 Assessment of safety

Adverse events will be recorded by self completion daily diaries (parent or child) which will be collected four weekly and GP records which will be examined at the end of the 24 months follow up period. Expected adverse events include infection, haemorrhage and pain following tonsillectomy with possible hospital readmission as well as sore throat, nausea, fever and dysphagia.

For the purposes of this study no reporting of serious adverse events is required. All adverse events will be managed as per normal care, since the intervention process of this study does not deviate from normal care.

## 13 Ethical considerations

The conduct of this study will be in accordance with the ethical principles set out in the Declaration of Helsinki.

The trial has approval from MREC and all the associated LRECs. The trial also holds a Clinical Trial Authorisation from the MHRA. The trial has NHS R&D and Caldicott Guardian approval from each participating site. There are no particular ethical problems with this trial. The ethical challenge is as with any surgical randomised trial where one arm is an irreversible procedure under general anaesthesia and the other limb effectively maintenance of the status quo with reverting to surgery an outstanding choice. Set against the surgical risk, however, is the essentially 'curative' nature of the intervention – no tonsillitis can occur once the tonsils have been removed. Further, the children under consideration all have qualifying levels of sore throat and would otherwise be eligible for surgery. In other words the issue is more the withholding of tonsillectomy rather than one of random allocation to intervention.

All subjects will provide written informed consent before any study procedures are carried out and a participant information sheet will be provided. As part of the consent process participants must agree to researchers & regulatory representatives having access to their medical records. Participants will also be informed that they have the right to withdraw from the study at any time.

## 14 Financing and insurance

The NHS 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.

## 15 Reporting and dissemination

A final report will be produced on completion of the study which will also be made available on the IHS web site. All consultants, research nurses and participating patients will receive a summary of the main outcomes of the trial. Where possible ongoing progress and results will be presented at appropriate conferences. Attempts will also be made to publish the study in academic peer reviewed journals as well as relevant newsletters.

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# 17 Appendices

## Appendix 1: Protocol Amendment 1, 2, 3 & 4

### Title

Amended from NESTAC: North of England Study of Tonsillectomy and Adeno-tonsillectomy in Children to NESSTAC North of England and Scotland Study of Tonsillectomy and Adeno-tonsillectomy in Children with the addition of Glasgow as a trial site. (September 2004)

### Contacts

Alessandra Vanoli left the University. (December 2005). Cheryl Wiscombe replaced Mary Dickinson as Trial Administrator. (August 2005). Katie Lock replaced Katie Brittain as Trial Manager. (August 2004). Katie Brittain replaced Nicki Rousseau as Trial Manager. (January 2002)

### Inclusion criteria

Amended from children (or carers) reporting experience of mild symptoms, 6 or more episodes within 2 years or 8 or more episodes within 1 year, and children reporting experience of moderate symptoms (sore throat for 5 days or more), 6 or more episodes within 2 years or 6 or more within 1 year to children (or carers) reporting experience of 4 or more episodes of sore throat within each of 2 years or 6 or more episodes of sore throat within 1 year. In order to increase recruitment to the trial. (May 2004)

### Exclusion criteria

Amended from children will be excluded if they require hospitalisation due to tonsillitis or quinsy; have obstructive symptoms suggestive of clinically significant sleep apnoea syndrome or rare medical conditions such as glomerulonephritis or Henoch Schonlein purpura; or have previously had a tonsillectomy; or have suspected velopharyngeal insufficiency to Children will be excluded if they require hospitalisation due to quinsy; have obstructive symptoms suggestive of clinically significant sleep apnoea syndrome, have rare medical conditions such as glomerulonephritis or Henoch Schonlein purpura; have previously had a tonsillectomy; have suspected velopharyngeal insufficiency, have co-morbidity that means they are unable to undergo the operation within the next 6 months, have a bleeding disorder, or have congenital/valvular heart disease in order to increase safety. (May 2004)

### Setting

Two additional centres Yorkhill Royal Hospital for Sick Children, Glasgow and Bradford Royal Infirmary added. (September 2004)

### Project timetable

Extension of the project from 5 to 7 years following poor patients recruitment. (July 2004)

### Data monitoring

A Trial Steering Committee was formed. (January 2004)

### Measuring participants' preferences and utilities

Details regarding this sub study were added as Appendix 2. (March 2006). Amendments were made to this sub study following pre-pilot work (November 2007)

### Data to be collected

Postal questionnaires become interview administered. (October 2006)

### Sponsor

Sponsor changed from Department of Health to Newcastle upon Tyne Hospitals NHS Foundation Trust. (August 2007)

### Study Centre

The Centre for Health Services Research, University of Newcastle upon Tyne became The Institute of Health and Society, Newcastle University. (October 2006)

# Appendix 2: Measuring participants' preferences and utilities

## Background

Recurrent sore throats and tonsillitis are commonly experienced in childhood (98.7%), with the majority of children having more than 4 episodes of sore throats annually[1]. There is currently no clear evidence on the best treatment option for recurrent sore throats and tonsillitis. Current treatments include pharmacotherapy or surgery. Parents of children who have undergone tonsillectomy tend to report a net improvement in children's condition, even though systematic reviews of the few clinical studies conducted so far do not show any significant clinical improvement in terms of severity and frequency of infections[2;3]. The literature has highlighted that parental enthusiasm for tonsillectomy is dictated by their perceived improvement in health-related quality of life dimensions, such as behaviour, general wellbeing, growth and sleep[4]. Very little empirical data is available on preferences for health states related to sore throats and tonsillitis. Given the high prevalence, morbidity rates and conspicuous resource implications at both NHS and individual levels, the issue of improving insights into the sets of outcomes on which to base treatment decisions becomes of public health relevance. Investigators have highlighted the need to inform parents about the clinical effectiveness of tonsillectomy, and to obtain their informed values about the (perceived) benefits of the procedure weighted against its morbidity[3]. The measurement of parents' preferences for alternative non-surgical management and likelihood of adverse events is also important.

## Objectives

- To establish the optimal treatment strategy from the perspective of parents in terms of their expected utility, and to determine to what extent this is preferred over its alternative;
- To ascertain whether and to what extent the (dis) benefits elicited from parents for tonsillitis is affected by the number of recurrent episodes (and their duration);
- To ascertain whether the parental decision making process is different from the one expressed by older children and, if yes, why and to what extent they are different;
- To provide insight into informed and shared medical choice models.

## Methods

Older children's and carers' values will be used to elicit preferences for trade-off between the perceived risks and benefits of surgery versus drugs treatment for sore throats and tonsillitis. Preferences will relate to scenarios associated with morbidity and quality of life because of symptoms and treatment complications. The scenarios are based on the health outcomes and quality of life domains relevant to the problem. Interviews will be carried out with a sample of older children and carers from 2 of the otolaryngology departments (Newcastle and Glasgow) and the Standard Gamble method[5] will be used to derive utilities weights.

## The Standard Gamble Method

Standard gamble is a technique used to elicit individuals' preferences. It is based on the axioms of expected utility theory[6] which therefore means we are measuring preferences under uncertainty. Standard gamble can be used to measure health state preferences for chronic or temporary health states. For chronic health states individuals are asked to value living with a health state for the rest of their lives. For a temporary health state individuals are asked to value the health state assuming they had to live in it for a specified period of time. To measure individuals' preferences for a chronic health state they are offered a choice between two alternatives. Alternative 1 is some form of treatment that has two possible outcomes; a return to full health for the rest of their life or immediate death. Alternative 2 is a certain outcome of remaining in the chronic health state for the rest of your life.

The standard gamble method of preference elicitation can be difficult for many people to understand as most people do not usually express their preferences in terms of probabilities. For this reason when conducting the interviews a visual aid known as a chance board can be used[5]. The chance board is used to present to people probabilities of 2 uncertain outcomes and 1 certain outcome. The board is divided into 2 sections. The top half of the board illustrates the uncertain Choice A (Alternative 1) with probability, p, of the most preferred health state and 1-p of the least preferred health state. Two small windows in this part of the board show what p and 1-p are. The probabilities can be changed by turning the wheel underneath the board. On the bottom part of the board is the certain outcome Choice B (Alternative 2). The health state placed in this section relate to symptoms which characterise tonsillectomy. The chance board converts the probabilities in to a percentage risk of an event (return to full health, immediate death or health state i) occurring. This is more understandable to most people. To begin with the chance board is set at a 90% chance of the preferred health state (returning to full health) and a 10% chance of the least preferred health state (immediate death). The individual then makes a choice between Choice A or Choice B. The probabilities are then altered using a ping-pong strategy, this is where the probabilities are alternated back and forth between a low value and a high value until the individual is indifferent between Choice A and Choice B. Using a ping-pong strategy reduces the possibility of anchoring bias. It also reduces the risk of a framing effect caused by the individual believing the increases or decreases in probability are gains and losses subject to a reference point. The percentages on the chance board convert to the probabilities for p and 1-p. The probability at the point where the individual is indifferent between Choice A and Choice B is the utility value of the health state described in Choice B.

As standard gamble is based on expected utility theory it is the preferred technique for preference elicitation by many economists. It has been claimed that uncertainty in the decision making process mirrors the clinical decision making process where doctors and patients must make choices under uncertainty[7]. However it could also be argued that the decision making process in health care is much more complicated than that described by a simple standard gamble question where there are only 2 outcomes and it is centred around full health and death. In a typical clinical decision there will be multiple outcomes with less wide ranging effects than full health and immediate death. The standard gamble method has a number of problems associated with it. The main problem is that it is cognitively demanding as many people are not familiar with expressing their preferences as probabilities. Therefore it may produce results which do not match individual's true valuations. Also many people are risk averse when it comes to their health and so will always choose to remain in state i (the certain outcome) no matter how bad it may be rather than take the gamble. This has lead to higher reported utility values for standard gamble compared with valuations produced by time trade off and the visual analogue scale.

**Study sample**

The sample will consist of consenting participants from 2 of the otolaryngology departments (Newcastle and Glasgow).

*Inclusion criteria for children:*

- Children aged 12 to 15
- Any gender
- Any nationality (interpretation services will be sought where appropriate)
- Experience of at least one episode of sore throat in the last 12 months, which required medical attention

*Inclusion criteria for parents/carers:*

- One of the parents (or carers) of children aged between 4 and 15 years, who had experience of at least one episode of sore throat in the last 12 months, which required medical attention
- Any age
- Any gender
- Any nationality (interpretation services will be sought where appropriate)

*Exclusion criteria for children/parents:*

Unable to communicate

Learning difficulties

The aim is to elicit utilities from the perspective of the parents, since they are the medical decision-makers for the child[8]. We assume that within a parental relationship, the 'principal-agent' model holds, i.e. the parents prefer the treatment which they believe to be in their child's best interest. Sensibly, we assume that children do not have a clear discernment between alternative treatments and outcomes, and therefore they will unavoidable rely on their parents' decisions. However, since older children (12+) are more mature and have more capabilities to make abstract thoughts and use complex language[8], their utility values will also be elicited, and compared with those of the parents. This will allow us to test the agency model against the alternative hypothesis that parents aim to maximise their own utility function, including, in addition to the arguments of the child's utility function, factors such as the impact of the disease on the use of their own time and emotional status[9], or the satisfaction of their own deep psychological needs[10].

**Sample size and recruitment process**

A sample of 100 parents and 100 older children from 2 of the otolaryngology departments (Newcastle and Glasgow) will be telephoned and asked whether they will be willing to take part in the utility study. Interviews will take place at a mutually convenient place and time after the agreed course of treatment.

**Development of scenarios**

Scenarios describe the relevant outcomes. The process of scenario building is informed by the type of events, duration/frequency of events. This information has been derived from a review of the literature. Scenarios are outlined below.

**The interview process**

An interviewer's handbook and response booklet (i.e. a response marking form) have been prepared and are enclosed together with a consent form and information sheet. Interviews will be initially pre-tested with IHS staff, therefore a pilot study will be conducted before the main study on 4 or 5 pairs of parents and children aged 12-16. Interviews from the pilot study will be checked to ensure quality and standardisation of the interview process. Interviews for the pilot and main study will not be taped.

**Analysis strategy**

Data will be collected on the utility scores of two health states estimated using standard gamble. Basic demographic data will be also be collected. Frequencies of the structure of the sample such as the male/female ratio and parent/own value ratio will be produced along with frequencies of the characteristics of the respondents such as stage of illness and socio economic status. The mean age of the sample will also be estimated. The mean utility values for each of the health states estimated using standard gamble will be calculated for the whole of the sample.

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**NESSTAC Scenarios for utility study [for parents]**

## Health state X

Your child gets 6-7 sore throats each year. These last 7 to 10 days each.

During this time your child...

- finds it hurts to swallow
- has a temperature, headache, earache
- feels sick and eats less.
- takes antibiotics and pain killers which may give them diarrhoea and a skin rash. After the first 5 days these symptoms begin to improve.
- has time off school, when they go back they are behind with the work.
- cannot take part in family, group or sporting activities.
- feels ill and is tired and irritable and may argue with you and your family.
- You are worried about them and may not be able to go to work or carry out your normal activities.

## Health State Z

**For up to 2 weeks after the treatment your child…**

- Has a sore throat
- Feels sick
- Has a temperature
- Tired and irritable
- Small risk (1 in 20) that the tonsils will bleed and they have to have a blood transfusion
- Cannot go to school
- Cannot take part in family, group or sporting activities
- May wake up in the night
- You are worried and have to stay off work to look after them

**After the first 2 weeks your child….**

- Has 1-2 sore throats each year. These last 2-3 days each
- Has 2-3 days off school each year when they have a sore throat
- Feels ill and is tired and irritable when they have a sore throat
- You may have to take time off work when they have a sore throat
- When they do not have a sore throat your child has no pain or discomfort, behaves normally and can take part in their normal activities.

## Good health

Your child…

- has no pain or discomfort and is full of energy.

- behaves normally at home and school.
- can go to school and join in classes
- is able to join in family, group or sporting activities.
- You have no worries about their health. You are able to carry out your normal activities.

**NESSTAC Scenarios for utility study [for 12-15 year olds]**

**Health state X**

- You get 6-7 sore throats each year. These last 7-10 days each.

During this time…

- It hurts to swallow
- You have a temperature
- Headache
- Feel sick and eat less
- Take antibiotics which can give you diarrhoea and a rash
- You feel tired and irritable
- Cannot go to school
- Cannot do your usual activities
- Your parents are worried about you and may not be able to go to work.

**Health State Z**

**For up to 2 weeks after the treatment you …**

- Have a sore throat
- Feel sick
- Have a temperature
- Feel tired and bad-tempered
- Small risk (1 in 20) that the tonsils will bleed and you have to have a blood transfusion
- Cannot go to school
- Cannot take part in family, group or sporting activities
- May wake up in the night
- Your parents are more worried and have to stay off work to look after you

**After the first 2 weeks you ….**

- Have 1-2 sore throats each year. These last 2-3 days each
- Have 2-3 days off school each year when you have a sore throat
- Feel ill and tired and bad-tempered when you have a sore throat
- You parents may have to take time off work when you have a sore throat
- When you do not have a sore throat you have no pain or discomfort, behave normally and can take part in your normal activities.

**Good health**

- no pain or discomfort and you are full of energy.
- behave normally at home and school.
- able to go to school and to join in classes
- join in family, group or sporting activities.
- Your parents go to work and carry out their normal activities.