NETSCC, HTA

21 March 2012

An open randomised study of autoinflation in 4-11 year old school children with otitis media with effusion (OME) in primary care (AIRs: AutoInflation Randomised study)

Version 5, 25-08-11

Ethics Reference:	09/H0504/75
Sponsor Reference	6415
Funder Reference	09/01/27
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Funder :	NIHR HTA
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Date:	20.10.11

Primary Care Clinical Trials Unit

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ABBREVIATIONS

ANCOVA	Analysis of Covariance
AOM	Acute Otitis Media
BNF	British National Formulary
CI	Confidence Intervals
CSG	Clinical Study Group
DMC	Data Monitoring Committee
DoH	Department of Health
FAQ	Frequently asked questions
GCP	Good Clinical Practice
GNOME	GPRF study into nasal steroids for OME
HUI	Health Utilities Index
ICER	Incremental Cost Effectiveness Ratio
ICH	International Conference on Harmonisation
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
OME	Otitits Media with Effusion
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse
TADAST	Two alternative Auditory Disability And Speech reception Test
TMG	Trial Management Group
TSC	Trial Steering Committee

SYNOPSIS

Study Title	An open randomised study of autoinflation in 4-11 year old school children with otitis media with effusion (OME) in primary care. (AIRs**: A**uto**I**nflation **R**andomised **s**tudy)
Internal ref. no.	09/01/27
Study Design	Open randomised controlled trial with two arms: autoinflation and standard care
Study Participants	School children aged 4-11 years old with glue ear in at least one ear
Number of Participants	294
Planned Study Period	Pilot study: July 2010 to December 2010 Main study: 3 years duration
Primary Objective	Assess the clinical effectiveness of autoinflation in resolving OME at 1 month
Secondary Objectives	• Assess the clinical effectiveness of autoinflation in resolving OME at 3 months • Assess the cost effectiveness of autoinflation: in terms of the cost per additional child achieving resolution of OME at 1 and 3 months; and also in terms of cost per QALY. • Describe the experience of using autoinflation, including nurse observed competence and reported compliance and develop an easy to use training protocol for every day practice.
Primary Endpoint	• Tympanometric resolution in at least one affected ear per child at 1 month, defined as conversion of the B-type highly predictive of effusion to either an A or C1 type i.e. back to normal pressures.
Secondary Endpoints	• Study specific questionnaire at 1 and 3 months, weekly diaries up to 3 months (to record days with reported hearing loss and earache, as well as recording periods of remission and recurrence) • Tympanometric resolution in at least one affected ear per child at 3 months, defined as conversion of the B-type highly predictive of effusion to either an A or C1 type i.e. back to normal pressures. • OMQ-14 a functional health status measure andstudy specific questionnaire of NHS resource use - self-administered at 3

	months, Health Utilities Index at 1 and 3 months plus a study specific questionnaire on health resource use including recurrence, referral etc at 6 months. • Short study-specific questionnaires at 1 and 3 months to evaluate compliance, positives/negatives of device. Record of nurse assessments at 1 and 3 months.
Intervention	Autoinflation

1. PLANNED INVESTIGATION

1.1 Aim

The main aim of this proposed randomised study is to evaluate whether a standard manufactured autoinflation device (Otovent) is an effective treatment for OME ("glue ear") in children in an NHS primary care setting. Instruction and support in use of the device will be given to both parent and child but is limited to a brief intervention which could be feasibly delivered by a primary care nurse. The main clinical outcome is resolution of OME assessed objectively by tympanometry.

1.2 Research objectives

i). Assess the clinical effectiveness of autoinflation in resolving OME at 1 month (primary outcome) and 3 months (secondary outcome).

ii). Assess the cost effectiveness of autoinflation: in terms of the cost per additional child achieving resolution of OME at 1 and 3 months; and also in terms of cost per QALY.

iii). Describe the experience of using autoinflation, including nurse observed competence and reported compliance and develop an easy to use training protocol for every day practice.

1.3 Design

The proposed design is a pragmatic two-arm trial. Children randomised to the intervention group will start Otovent treatment immediately, whilst treatment in the control group will be delayed until the end of a 3 month comparison period. Children in both trial groups will undergo tympanometry at baseline, 1 and 3 months but usual clinical care will not be otherwise constrained. In the intervention group, children with normal tympanometry in both ears at 1 month will discontinue autoinflation whilst those with persisting OME will be encouraged to continue for up to two further months.

The intervention will be offered to control children with residual tympanic dysfunction at the end of the 3 month comparison period as we believe it will substantially increase recruitment to the study.
The main study period up to 3 months will evaluate the additional benefit over usual care of a standardised purpose manufactured autoinflation device (Otovent) in improving OME, in school aged children in primary care, as assessed by a more objective method (tympanometric resolution) than history, at both1 and 3 months.

We will assess cost effectiveness at the end of the randomised 3 month active monitoring period as the health economic main outcome in terms of costs and QALYs, and will also include resolution of OME in the shorter term (1 month), and use an extrapolated scenario analysis including the data from the 6 month audit for longer term projections of costs.

A period of three months active monitoring (watchful waiting) has been chosen as it is best current practice. Good clinical practice also requires that children deemed as severe or protracted at the outset may need to be referred for surgery immediately and excluded from the trial; it is envisaged that this group will be very small.

2. EXISTING RESEARCH

2.1 Introduction

Otitis Media with Effusion (OME) is the commonest chronic condition of childhood and the commonest reason for childhood surgery. It is a collection of fluid behind the ear drum without inflammatory signs, [1] and when present for 6 weeks or more is often called "glue-ear". OME can lead to significant hearing losses, especially when both ears are affected, and may have a significant and wide impact on the child's life and development.[2,3,4]

The majority of children are seen in general practice, approximately 130,000 per year.[5] A further analysis of these General Practice Research Database records up to 2008 suggests that the incidence for all types of otitis media in children has stabilised since 2001.[6] By the age of 4 years, as many as 80% of children will have had at least one episode of OME. Most episodes resolve naturally with an average duration of 6-10 weeks, with just 10% of episodes lasting a year or more.[4,5,7,8] Within the broad picture of the natural history there are a substantial number of children that do not have effusions that resolve quickly, remain a cause for concern, pose management issues for general practice, contribute to quite variable referral rates, and leads to surgery in about 1-5 per 1000 children per year (grommets).[9] The scale of the problem of OME in society is likely to increase in the near future. Firstly as an anticipated sequelae of influenza in children,[8] and secondly a 2009 Office of National Statistics report has highlighted a rise in the UK fertility (birth) rate from a record low in 2001(1.63) to a record high in 2008 (1.96).[10] These factors are likely to lead to an increased clinical load in the near future, and thus makes the search for evidence for pragmatic interventions for OME in primary care both timely and apposite.

A recent NICE review has found no proven effective medical treatments that are applicable in primary care.[11] Because OME might usually be expected to resolve naturally, watchful waiting for 3 months or *active monitoring* as it is better described, is now an established clinical recommendation.[11,12,13] Active monitoring of affected children might be performed in either primary or secondary care, although it has been questioned if GPs have the techniques for active monitoring with only about 5% of practices having the equipment, and also whether use of tympanometry in this setting would also lead to over referral.[14] However a recent study in primary care from our group has demonstrated that with appropriate training tympanometry is eminently feasible in this setting with low referral rates observed.[15] During periods of reasonable expectation of natural resolution of the condition, temporising medical management is frequently given in general practice, and this often includes antibiotics, decongestants, and anti-histamines, all of which have been shown to be clinically ineffective. Furthermore these interventions are associated with substantial NHS costs and a number of

harms and other disadvantages.[11] A recent large study of topical intranasal corticosteroids for 3months in children aged 4-11 years has also proved an ineffective method of temporising treatment in a primary care setting.[15] Clinical trial evidence for an effective non-surgical intervention that could be applied in primary care where the majority of children are initially seen and managed thus remains an important research priority. A low cost, safe and effective treatment applicable in primary care, could also serve to benefit by improving patient and parent satisfaction, and general adherence with and support for the recommended monitoring process. The simple autoinflation treatment that is proposed in this trial has no known harms to date, and has potential to provide three important health benefits: i) a reduction in antibiotic prescribing and consequent risk of antibiotic resistance,[16,17] ii) a reduction in hospital referral and need for grommet surgery,[11,13]; iii) a reduction in potential learning problems from deafness associated with OME and tympanosclerosis associated with surgery.[3,18,19]

2.2 Clinical trial evidence for autoinflation

Autoinflation is a promising technique with some preliminary efficacy and effectiveness demonstrated in several small hospital based trials reported in two meta-analyses.[20,21] In total 6 clinical trials were found suitable to be included in Cochrane.[22-27] A literature search (search date March 2009) ,which is an update of the original Cochrane systematic review , has been performed using the standard Cochrane search method as described in full in reference 20. Two additional references to clinical trials were found of which one was a completed RCT carried out on a total sample of 40 children.[28] Good results were shown in the compliant group from one small hospital study that involved a total of 85 children aged 3-10 years.[22] Different methods of autoinflation using Valsalva techniques, party blowers, and face masks as well as purpose manufactured devices are considered in both meta-analyses. The balloon technique (Otovent) and the Ear popper™ (operating like a syringe driver applied to the nose) are the only two purpose manufactured standardised delivery devices and appear also to be the most promising studies so far in terms of beneficial odds ratios. Four small studies used the balloon technique (Otovent) intervention as the method for autoinflation. One was an independent study done in UK secondary care,[22] one was based on a Danish sample,[23] a third hospital study remains unpublished (Suonpaa and Grenman). Combining these three trials with the most recent small trial,[28] gives a combined potentially homogeneous total of 336 children, but dominated by secondary care studies. For the tympanometric outcomes at 1 month the odds ratio based on all four studies was 2.4, but was not significant. The Cochrane authors although finding a large effect size for the autoinflation method overall with a Relative Risk of Improvement of 2.47 for tympanometric outcomes reported confidence intervals going through1 (0.93 to 6.8). The authors concluded there was insufficient evidence as yet to recommend widespread use in general practice, and called for a larger-scale pragmatic trial with longer term follow-up than 1 month.[20]

A subsequent up to date (Sep 11, 2009) Medline search has revealed no further relevant studies. Thus the clinical efficacy and effectiveness of autoinflation in a primary care UK population remains untested and requires full evaluation before use in the NHS. Primary care is the best setting to evaluate effectiveness of autoinflation, because most children with OME are seen in primary care, it is increasingly clear that there are as yet no satisfactory treatments in this setting,[11,15,29,30] and lack of a good non-surgical intervention is

probably a major factor fuelling the substantial rates of referral for childhood surgery, which is thus far the only proven effective treatment.[13] There are no known harms associated with autoinflation, with higher respiratory tract infection rates noted in the control groups in two studies, making it unlikely that the increased pressure in the nose during autoinflation spreads infections.[22,23] Perhaps compliance is the major potential weakness with this technique, and it can probably only reliably be performed in school aged children (4-5 years and older). Autoinflation by Otovent (£7) has the advantage of being considerably less costly than the Ear popper ($200) and with better preliminary evidence than just the 1 manufacturer randomised study in 94 children for the ear popper,[24] thus making the nasal balloon method the intervention of choice for further evaluation. No clinical trial evaluation of the treatment method (autoinflation), which has considerable pragmatic potential to help a great many children, has been done thus far from any primary care setting, with the few studies to date all being small and hospital based.[22-28] If anything the effect size in primary care is likely to be larger than in secondary care due to the nature of the effusion (see mechanism considerations below).

In summary, the current evidence suggests there may be a 2.4 times higher rate of short-term tympanometric cure in children using a purpose manufactured balloon (Otovent device) than in controls.[20,28] The combined studies however did not provide a definitive answer, all lacked intermediate and long-term follow up, and were investigated in largely selected secondary care populations.

2.3 A description of the technology; some mechanism considerations; and possible effect on health status.

Autoinflation is a self administered method that aims to insufflate the Eustachian tubes with air, improves tubal ventilation and corrects the negative middle ear pressures often observed in children with glue ear - thus leading to recovery. Autoinflation has probably been done in some form from antiquity most likely as the Valsalva manoeuvre. This is done by trying to do a forced exhalation by contracting the diaphragm and abdominal muscles when the mouth is closed and the nose pinched to try and make the ears “pop” as done by divers or on aeroplanes to equalise the pressure in the ear with atmospheric pressure. Not all children can do this and the most promising way for children to autoinflate effectively is probably by blowing up a balloon through the nostril. This must be done regularly (e.g. x2 or x3 times each day) according to trial evidence, with careful and appropriate training of guardians and children required.

The proposed study technique involves blowing out through each nostril in turn into a purpose fitted connector device (nasal tip or nozzle) with a balloon attached. The pressure generated to inflate the balloon is equivalent to about 30 inches of water pressure, and aids passive opening of the Eustachian tubes (the critical opening pressure required to introduce air into the middle ear reduces as the dimensions of the Eustachian orifice increases with the child’s age, so the technique is likely to be more effective in older children as well as easier to do). The introduction of air into the middle ear has been shown to improve or normalise negative middle ear pressure in children performing the technique.[23]

The observed transience of improved pressure changes in the middle ear from the autoinflation method has been questioned as a sufficiently adequate explanation for any therapeutic mechanism, with what appears to be singular theoretical reliance on restoration of tubal function (for a condition of mixed aetiology).[33] The beneficial effects of changes in gas composition e.g. of small rises in oxygen tension in the middle ear (associated with improved middle ear ventilation over time), may also be theoretically important however, and may fit with ongoing research into the role of hypoxia in some genotypes, in particular the MRC Jeff mouse genetic model of otitis media. Autoinflation may also improve natural drainage by dislodging any mucus plugs blocking the Eustachian tubes etc. The clinical trial evidence to date supports a distinct therapeutic effect from autoinflation in compliant groups, however unclear the theoretical mechanism (this also holds true for OME causation in general). A clinical trial applied earlier in the natural history in primary rather than secondary care (where effusions have developed to be more mucoid and tenacious) is *prima facie* more likely to be effective using this aerating technique and in preventing sequelae. Along with severity, relevant effect modifiers for this method may include child age/head size, and compliance frequency.[15,22,23] Season was not found to be an effect modifier in a primary care study.[15]

Otovent is already available on NHS FP10 prescriptions (cost £7.20 per month for adults, with children exempt). If the short-term cure suggested in the Cochrane review were realisable in everyday practice (see power calculation), our hypothesised estimate of the potential effect on health and clinical practice is a 70% reduction in antibiotic prescribing, a 30% reduction in GP re-consultations, and 50% reduction in hospital referrals with insertion of grommets.[4,11]

3. RESEARCH METHODS

3.1 Phase 1 pilot study.

The 12 month pilot study is already funded through the NIHR Primary Care School and is taking place in two Southampton area and two Oxford area practices over the coming Autumn/ Winter seasons of 2009/10. It is due to complete in April-July 2010. It is being performed because this is the first study of its type in primary care. We are using a moderate degree of new technology, *e.g.* tympanometry and a new mechanical technique for treatment in this setting. Also the new research practices require full training with the specific study material packages. The pilot aims for 28 children. We currently estimate uptake rates of 40% which we deem likely because all children confirmed with symptomatic and tympanometric OME will be offered a treatment and improved monitoring in addition to usual care (also there are no known side effects to this treatment). Basing the take-up on 40%, 112 children accepting screening from 280 invited through 4 practices, 25% of which will be eligible for randomisation on tympanometry will yield 28 children in the pilot trial. This pilot will allow confirmation of the trial uptake estimates of 40% with a 95% level of precision of ± 5.7%.

3.1.1 Progress with the pilot study

The necessary National Research Ethics Service full approval for both the pilot and main study has been received on the 10th August 2009 Ref 09/ H0504/75. All trial materials have been developed (including the manual) and adapted awaiting further operational feedback. Research Governance approval has also been given for phases 1 and 2; and the 4 practice training sessions with research nurses and teams have been completed this month (September 09).Supplies (100 packs) have been received from the company and have been distributed to the practices. We have obtained some preliminary parent feedback about use of autoinflation via company consumer feedback. A website (Otovent) http://www.gluear.co.uk supplies accurate patient information about using the balloons and has a high quality demonstration video (also available on You-Tube). A participant forum and FAQ are also on this website. We will recommend initial access to this site in the intervention arm, and for controls wishing to use it at 3 months.

3.1.2 Completed pilot study summary

The pilot work has i) demonstrated feasibility ii) demonstrated good study compliance with the technique and follow up iii) improved logistical assumptions e.g. trial uptake precision estimates, iv) provided useful consumer feedback, v) developed the study materials and information in a standard operating manual, vi) confirmed the original study power calculation and demonstrated a potential large effect size OR 4 95%CI 0.97 to 16.46, vii) added a new exclusion criterion viii) refined the randomisation method to be used to improve access- now web based with training support ix) developed a web based hearing disability outcome with evaluation of reliability for use as a trial outcome x) improved the trial management structure and costings.

3.2 Phase 2. Main Study

An open two arm randomised control trial of autoinflation in the treatment of OME in 4-11 year old children with assessment of effectiveness and cost-effectiveness at 1 month and 3 months (this application).

A large randomised pragmatic trial is needed to establish objectively short term clinical effectiveness (not known) and cost effectiveness at one month, and important NHS effectiveness and cost-effectiveness outcomes in the medium term at 3 months. This is both a usual and expedient time frame for the many children with OME episodes who are initially managed in primary care (we will use scenarios for longer term cost estimates).[11,15,20]

3.2.1 Setting

The research will be based in the community. The study will complete the pilot in Thames Valley, Hampshire, and Wiltshire regions first. The main study will be set within 40 GP practices; 20 each around the Southampton and Oxford centres. The GPs in each practice will act as the Principal Investigators and a Research Nurse will be assigned to each practice if one is not already in place. Practices will be recruited through the South West and South East Primary Care Research Networks.

3.2,2 Target population

Children aged 4-11 years, attending or just about to attend school will be identified through four routes:-

1. Parents of all children at increased risk of OME i.e. those aged 4, 5 and 6 years (high prevalence of OME, 10-30%)[8] will be identified from practice age sex registers, and will be sent an invitation letter and information sheet in the autumn in time to coincide with the high seasonal prevalence. The letter and information sheet will describe glue-ear and the symptoms it commonly produces. Where there are no specific OME related concerns in the past 3 months (highlighted on the invitation letter checklist) parents/guardians will be advised that a screening is not required. The letter will detail the purpose of the study, what it entails etc. and offer interested parents of symptomatic children up to two tympanometric screenings, one in the first or autumn term (Sept – Dec) and for those passing the tympanometry at this time (*i.e.* do not have at least one B reading) a second screen offer will be made for the spring term (Jan - Apr). Should asymptomatic children go on to develop suggestive symptoms over the study period *e.g.* develop an ear infection, hearing or speech concerns etc. an opportunistic screening will be arranged directly.
2. A Research Nurse (RN) will audit the notes of all 7-11 year old children using Read codes to identify those having attended the practice with any ear related problems in the previous year. These children will then be invited for a targeted screen using an appropriate invitation letter to guardian and child (checking not to duplicate invitation).
3. A clinical opportunistic case finding approach will be used where each participating practice will be alerted to the ongoing study and all GPs, nurses, health visitors etc will refer on suspected new cases to the research nurse.
4. Links may be made with the local school nurses for any suspected participating practice registered incident cases they see to be informed about the study.

3.2.3 Recruitment procedures (see Appendices 1 and 2)

For parents accepting the invitation for screening of their children, the research nurse will make an appointment for them and their child to be seen. At this initial appointment the research nurse will go through the study and information sheet, answer any questions etc. Full informed consent will then be taken for those parents wishing their child to be screened, and assent will be taken from the children. (Information sheets and consent/assent forms will be used for each age group; 4-6 years old and 7+ year olds).

The research nurse will first use otoscopy (we will ensure access to good quality otoscopes) to check for any obstructing wax, perforations etc., before performing the tympanometry on both ears. The modified Jerger classification will be used.[15,34,35] The findings will be explained to the parents and children, and any child with a relevant symptom history and at least one ear with a B tympanogram will be invited to take part in the study. Those wishing to participate will be randomised 50:50 by a web based randomisation method to either standard care by their practice (*i.e.* the usual care unaffected by being in the study) plus autoinflation for 1 to 3 months, or standard care alone by their practice for 3 months. It will be explained to the standard care only group that if after three months their child's ears have not got any better (estimate about 50% chance of cure overall for uni and bilateral cases combined by 3 months in controls)[15] they can receive autoinflation if they so

wish (for trial follow -up period 3-6 months). This as previously stated, should improve recruitment rates into the study, which have been refined by the pilot, and should furthermore encourage the active monitoring process for control children up to 3 months including those where there is no initial resolution at 1 month. Parents from each arm will be asked to complete the OMQ-14 functional health status questionnaire that bests predicts QoL (to assess baseline severity in a standardised manner), and also complete a short study-specific questionnaire. The participants will also be given a weekly symptom diary to complete (for 1 month at the first visit, and 2 months at the second visit). Symptom diaries are based on measures developed in the GNOME study and a previous Acute Otitis Media study.[15,36] Parents will also receive a daily check sheet to complete with their child to assess compliance, record ease of use and provide details of what treatment, if any they have used (see also outcomes section). NRES has suggested giving tokens for children as a reward e.g. Waterstones/HMV tokens, which both groups will receive at 1 and 3 months for returned completed diaries (£7.50 each, total £15), and should also help somewhat to offset travel etc. for families and so improve compliance. Hearing disability will be evaluated at baseline, and 1 month. Pure tone audiometry is not likely to be valid in the usual primary care setting, and history for hearing loss is only 71% sensitive.[11,15,37] Therefore nurses will instruct on use of a web based test: a forced choice two alternative auditory disability and speech reception test (TADAST), which is less prone to invalidation by back ground noise, is already in a standardised format, and was originally developed in primary care to assess children with glue ear.[38] The pilot has shown good test-retest repeatability of this new web version in 4-11 year old children (medical student project 2010).

Children randomised to receive autoinflation will be shown by the research nurse how to perform autoinflation. The guardian will also be involved to demonstrate use of the balloon for the child to copy, to improve compliance. When the balloon has thus been stretched sufficiently through use, the child will be encouraged to blow up the balloon for themselves, firstly through the mouth, then by blowing out through their nose. Recipients will be provided with the nasal fitting device, with 5 balloons per trial intervention pack, containing pictorial and written instructions on correct use. Additional website and You-Tube address details will be supplied so that children and parents can watch a video of the method whenever they choose, to provide support on correct performance of the technique. Micro-tympanometry will also be done immediately after per-nasal inflation of the balloon to record the tympanogram type, either A, C1, C2, or B (a sequence of increasing severity). This is being done to see if any immediate conversion of tympanogram type to one of improved middle ear pressure predicts results at 1 month. Parents will be phoned at home by the nurse after 2-4 days, primarily as a supportive measure with the nurse providing any additional requested information for parents and children that should also encourage compliance. The nurse will take note of any untoward effects and discuss any queries or issues. Where compliance is reported as unsatisfactory a second nurse appointment will be offered, when the child and guardian can be given further specific pragmatic tips and education about improving the technique based directly on observation of use. (Prof. Stangerup has provided useful practical advice on procedures which we have implemented in the pilot). After 1 month those not cured using tympanometric criteria in the intervention arm will be encouraged to use a further 2 months course of balloons for autoinflation, supplied in 2 boxes.

3.2.4 Randomisation

If the trained research nurse assesses that the child is likely to be able to use the device they will be offered randomisation. To ensure the generator and executor processes are fully independent in relation to randomisation (and avoid subversion) we will employ an external agency to provide a web-based randomised selection method to participating trial nurses who will access a preloaded website on their computer. Nurses will be trained in use of the website and have further access to support. Randomisation will be overseen by the Primary Care Clinical Trial Unit located at Oxford. A standard minimisation protocol will be used based on three potentially important variables: age (>=6.5 years versus <6.5 years); baseline severity (1 versus 2 B type tympanograms); and gender.[15]

3.3 Justification of an open pragmatic trial

Because of the nature of the procedure use of a placebo and blinding are not possible. However effectiveness outcomes for the NHS are best measured by such a method, and will reflect real life outcomes. The use of an objective primary outcome - tympanometric cure, one that is also independently verifiable, will reduce potential subjective biases in the study. We will use faxes of tympanograms to the main co-ordinating centre to improve validity of this outcome and check correct categorisation of baseline, one and three month recordings. We will estimate placebo effects of using the device by asking how effective parents and children believed the device to be at 2-4 days.

3.4 Intervention being assessed

The intervention has two elements: the prescribing of the device, and provision of brief training/support, with the latter designed explicitly to be generalisable to everyday general practice.

The use of the purpose manufactured device (Otovent) will be evaluated as supplied to the trial by Kestrel Medical Ltd. Poole, Dorset. One standard pack containing the nasal tip- a safe spherical connecting device made of plastic and 5 quality checked latex balloons. Packs will be provided to those randomised to the immediate autoinflation treatment group. One pack will cover 1 month of treatment due to decreasing elasticity of each balloon over about a weeks use. All children with a residual B tympanogram at 1 month will be offered 2 further standard packs to cover 2 further months of treatment. Uptake will be recorded for concordance/compliance considerations.

The child will be instructed to inflate the balloon once via each nostril in the morning, after school, and at bedtime (x6 total). A sticker book diary/wall chart will be provided for the children to encourage participation. All children will receive usual clinical care, and the intervention will be in addition to this. We intend to use practical delivery advice from other relevant trials[22,23] *e.g.* use of parents to demonstrate the method, use of the extended Valsalva manoeuvre and or Politzer equivalent, with use of step-wise techniques for very young children to help them to actually blow air through the nozzle first etc. The training and support element, whilst evidence-based and making use of secondary care expertise, is actually very simple, and encapsulated in a brief written protocol and manual which could be readily implemented by a nurse during a single consultation.

3.5 Protection against other sources of bias

The recruitment rate and practice demographics of responders/non-responders plus study refusals and documented reasons for these will be examined to evaluate the sample characteristics compared with a more general population. However we anticipate that recruitment will be high because all children will be offered an interesting potential new treatment and improved monitoring in addition to standard care. Careful attention to follow-up of all study patients at 1 and 3 months together with communication of goals will ensure minimal loss to follow up. Notes will be used for 6 months relevant costs e.g. referral.

Measurement bias will be minimised because trial outcomes used have already been assessed for validity in several large trials from our group GNOME,[15] a pragmatic trial of AOM,[36] and in collaboration with the MRC [2,15] We are assessing repeatability, construct, and criterion validity during the pilot phase of the OM questionnaire and also in another cross sectional survey to assess a new web test version of the two alternative 36 item forced choice auditory disability test -the TADAST.[38] The prototype test with restricted research access website www.tadast.soton.ac.uk has been installed Sep 2009. It has on line instructions for self completion, with an initial practise test section.

The autoinflation technique which in this instance is the “balloon blowing” method is easier and more reliable once children have reached the school age group and fun to do, which should minimise performance bias. Company website materials have also been developed to improve patient adherence and standardise the technique. The pilot will seek views from patients, nurses and GPs, to modify procedures and information, and maximise adherence to trial procedures, and should further help minimise performance bias. Both companies involved (Kestrel Medical – Otovent, and Starkey Laboratories - MTP10) have agreed to help with providing trial approved patient information and local research training days. We will ensure that all trial research nurses are trained in accordance with ICH-GCP guidelines and the necessary trial methods and techniques – see also main outcome section.

The main analysis will be on an intention to treat basis i.e. as randomised, to reduce attrition bias and improve generalisability of the sample. We will seek to minimise any loss to follow up in all groups. A per protocol secondary analysis to estimate effects due to compliance will also be performed. Because autoinflation is also available over the counter, possible contamination bias may occur due to use in the control arm, but will be explicity dealt with by asking patients guardians prior to randomisation to agree not to buy and use autoinflation devices for 3 months if randomised to the control arm. This effect should also be minimised by ensuring good patient/guardian and practice communication and education. Furthermore all patients may receive autoinflation by the end of 3 months as part of the trial if they so choose. At 3 months the guardians will be asked if Otovent was purchased independently to the study, or indeed if any other autoinflation device was used or tried. We will also remind patients and their families that currently Otovent is only recommended in children after they have first seen their own GP, and should be obtained on an FP10 prescription not obtained over the counter. We will ask research nurses to double-check if any “additional” Otovent was inadvertently prescribed in controls during the first 3 month period.

3.6 Inclusion criteria

- Aged 4-11 years and attending school at the time of the first planned tympanometric screen. (To be able to reliably perform the technique and have a greater theoretical chance of cure).
- A relevant notes recorded history of recent and or recurrent otitis media symptoms (defined as within the last year) **or** ear related problems in the previous year (e.g. suspected hearing loss, slow speech development etc.-audit terms specified); **or** a guardian denotes a concern in one or more OME related symptom domains* on the screening invitation letter symptom check list (in the targeted 4 to 7 years of age and seasonal high risk of OME groups).
- Tympanometric confirmation in a child of at least one B tympanogram (using the modified Jerger classification).This has a ~90% Positive Predictive Value of an effusion being present.[34] *i.e.* cases of unilateral or bilateral OME.

*Symptom lists have been developed from those reported in the GNOME trial, important OM8-30 symptom variables, and the recently updated Deafness Research UK 2009 parent information sheet about glue-ear, that also highlights typical symptoms *e.g.* speech concerns, mis-hears what is said, appears inattentive etc.

3.7 Exclusion criteria

- Children who need early referral as judged clinically, to include those known rarer cases with high risk of recurrence: Down's, cleft palate, Kartagener's, Primary Ciliary Dyskinesia, immunodeficiency states etc.
- 4 year old children not attending school at the time of screening, or children deemed by the nurse unable to comply with the technique of autoinflation.
- At study entry, children with a grommet already in place in an ear drum, or where the child has been referred or listed for ear surgery.
- Latex allergy (balloons are latex)
- A recent nose bleed in the past 3 weeks or more than one episode of nose bleeding over the past 6 months

3.8 Withdrawals

In accordance with recommended ethics practice guardians and children will be free to withdraw from the study at any time without affecting their usual high standard of medical care. Children in the autoinflation group will be advised to stop the intervention in the instance of any suspected related (expected or unexpected) serious adverse events. All children that do cease the intervention will be followed up (unless the parents withdraw consent) as this study an intention to treat analysis.

4. ETHICAL ARRANGEMENTS

This trial aims specifically to improve child health for this group of children and to establish the best non-surgical treatment for children with OME. Children are the main "consumer" group suffering from OME and its protracted effects, so adult studies (with a different aetiology and natural history) are inappropriate. As this trial will randomly allocate an additional treatment with preliminary evidence of effectiveness for the patient's condition as an adjunct to standard care, there will be no compromise of their care from the NHS. Trial support for clinical care with improved diagnostic monitoring should ensure exemplary clinical management during the NICE recommended active monitoring period (3 months).[11]

A qualified research nurse, used to working with children, will be given specific training in the trial protocol and will be provided with the trial manual. They will conduct all the trial procedures e.g. interviews and assessments, provide instructions etc. which will be minimally invasive (*e.g.* otoscopy, micro- tympanometry, web hearing disability test, study questionnaires). All trial staff (Research Nurses, Principal Investigators, the Chief Investigator and Trial Manager) will attend an approved ICH-Good Clinical Practice training session if they have not received training within the year prior to the main trial commencement date.

Children will only be involved after full informed consent is given. In accordance with National Research Ethics Service (NRES) guidance 6-11 year olds will be asked to give their assent after their parent/guardian has given consent. For the younger children (4-5 year olds) only the parent/guardian will be asked for consent, and no assent will be sought from these children. If a child refuses to participate or carry on, once consented into the trial their decision will always be respected. No pressure will be exerted on a child or their parent/guardian to participate nor will they receive financial benefit other than modestly priced book tokens for completing the diaries. There are several approved trial information sheets: a detailed one for the parents/guardians; one for 6-11 year olds and one for 4-5 year olds.

The NRES application form and trial documentation for the pilot and the main study were submitted to Southampton and South West Hampshire REC and received a favourable opinion in August 2009. As Otovent is a CE marked medical device, MHRA approval is not required. As for the pilot study site-specific Information forms have already been submitted and obtained for each pilot site contributing to the main study to cover local Site-Specific Assessment and for R&D requirements.

5. RISKS AND ANTICIPATED BENEFITS

As with all trials there is always a degree of risk to participants, however in this particular trial the risks are estimated to be extremely small. No side effects have been reported from current trials. The main theoretical side effect is an increase in upper respiratory infection due to air pressures generated in the nasal cavity equivalent to being submerged under 2-3 foot of water somehow spreading infected mucus up the Eustachian tubes. No such increase in infection rate has been noted in the trials so far and in fact the incidence of respiratory tract infection was observed to be higher in the control group in the only previous British study .[23]

The fact that fluid behind the ear on tympanometry is found less commonly in treated groups in most trials to date also means that ear infections are likely to be less when using the device. The ICH-GCP guidelines for definitions of adverse events/reactions will be followed, and all adverse events/reactions will be recorded. The co-ordinating centre's standard operating procedure for safety reporting in studies not involving an investigational medicinal product will be fully complied with, including reporting of all serious adverse events (*e.g.* any unplanned hospitalisation) to the sponsor immediately, and as will all related unexpected serious adverse events. In addition to any expedited reports, annual safety reports will be submitted to the main REC.

Placebo treatment is not planned at all in this children's study. All children/guardian participants will be offered the intervention after 3 months of the study if they were not initially randomised to the +autoinflation arm, and the fluid/effusion has not gone away by that time.

Using the combinations of:"natural cure+ standard care +/- any treatment effect from adjunctive use of the device," constitutes possibly the best primary care approach currently available to evaluate. On the basis of the NICE 2009 guideline which recommends active monitoring for OME for 3 months, and states "autoinflation may be beneficial in older children".[11] Although standard care will be fully detailed in the study there is no evidence for any significant effect of any of the commonly used treatments on tympanometric resolution. The level of trial care and aftercare will be thorough and, as proposed, will meet high standards.

5.1 Informing potential trial participants of possible benefits and known risks

In addition to the methods described under recruitment procedures, which will allow potential participants ample time to consider consent, we will provide a clear, appropriate and relevant information sheet for both children and guardians to consider the potential benefits and possible risks. With supplementary summary information available if requested (*e.g.* NICE summary[11] Cochrane review[20] etc)

6. RESEARCH GOVERNANCE

The sponsor is the University of Southampton. Agreements will be put in place between the sponsor and all participating sites outlining the roles and responsibilities of all parties. The trial will comply with the Data Protection Act 1998 and will comply with local issues required at each site. Non negligent harm will be covered by the University of Southampton and negligent harm will be covered by each GP practice's insurance Consumers will be involved at each stage of this trial - design, trial documents (*e.g.* consent forms, information sheets), conduct, analysis and reporting. The trial will be co-adopted by the Primary Care Research Network and the Medicines for Children Network (MCRN) and would become part of the latter's General Paediatrics Clinical Study Group (CSG). Following the MCRN's adoption of the GNOME study, the research team has had strong links with this network and this CSG from their inception.

A Trial Management Group (TMG) will meet regularly to review progress. A Data Monitoring Committee (DMC) will be established with a statistician and 1-2 other members who are independent of the study centre.

The DMC will review the data and any adverse events/reactions identified by GPs. A Trial Steering Committee (TSC) will be established with an independent chair and will meet regularly to ensure the trial is running to target, budget and time, and to resolve any issues incurred. A lay person will be invited to join the Trial Steering Committee to assist with the trial conduct, analysis and reporting.

6.1 Regulation compliance

This study will be conducted in accordance with the Research Governance Framework for Health and Social Care; the ICH-GCP guidelines and the updated version of the Declaration of Helsinki

6.2 Retention of trial documentation

Trial documentation in any study involving minors should be archived until 3 years after the youngest subject reaches 18 years old. Therefore all trial documentation for this study will be archived for 20 years to fulfil the above requirement in accordance with Good Research Practice (MRC 2005)

7. OUTCOME MEASURES

7.1 Main outcome

The primary outcome will be a tympanometric measure**.** Tympanometric resolution in ears will be defined as conversion of the B-type highly predictive of effusion to either an A or C1 type i.e. back to normal pressures. Type C2 will not be considered sufficiently cured or resolved because the PPV for effusion of C2 remains modest at 55%.[34]

The difference in proportions of children showing resolution to A or C1 in at least one B (affected) ear per child at one month is the main study outcome.

This outcome is chosen based on evidence from the Cochrane review and hence is the basis for the sample size calculation. It is also a robust outcome and less likely to be affected by any placebo effect of intervention. Otoscopy will be performed by the trained nurse prior to tympanometry to improve method validity. Nurses will attend a day course that includes full relevant instruction in practical tympanometry procedures and will use a learning-set of tympanogram print outs to categorise type before collecting data as a training aid. The MTP-10 micro-tympanometers used (sufficient stock is available from the recent GNOME trial) are being serially re-calibrated for the proposed new trial and all have a print out facility. A central trial fax-hotline will be used for tympanogram interpretation in the study for “at-point-of-care” support, and will be the basis for continuing training of operators to improve repeatability and validity of the method. (Tympanometric skills will be assessed in initial samples of consecutive cases per nurse-operator).

Difference in tympanometric baseline severity is likely to be an effect modifier and will be accounted for in both the minimisation protocol and secondary analysis (see relevant sections).

7.2 Secondary outcomes

All measures will be assessed at baseline (0), and 1 and 3 months post baseline (except the OMQ-14, designed to collect retrospective 3 month data and TADAST which will be performed at baseline and 1 month only).

- The difference in proportions of children showing resolution to A or C1 in at least one B (affected) ear per child at 3 months
- OMQ-14 a functional health status measure that is a derivative of the OM8-30 that is both pragmatic and predicts QoL well, and will be self-administered at baseline and 3 months (please see Appendix 2). The main measurement tools have been used in GNOME with validation.[15] The OMQ-14 is a succinct standardised and responsive 14 item measure that looks at the quality of life, physical and developmental impact of OME. It records the previous 3 month history including frequency of respiratory tract infections which is the main theoretical adverse event (see above). Together with a brief resource use questionnaire (used in GNOME) and notes audit, it will collect useful adjunctive health economic information.
- Parents will be asked to complete short study-specific questionnaires at the above times for evaluation of: compliance; positives/negatives of device; being in a study; NHS resource use for economic evaluation; and also use weekly symptom and adverse event diaries collected at 1 and 3 months to prospectively collect data on the main areas of OME clinical impact. The diaries record days with reported hearing loss and earache, as well as recording periods of remission and recurrence. The diaries make use of Likert scales for symptoms as validated and used in other studies from our group.[36,40,41]
- Hearing will also be assessed by using the web TADAST speech recognition in noise parent supervised (self-complete) test at baseline and 1 month.[38,42,43] Audiometry will not be included to assess hearing level in this trial because hearing level is not a known effect modifier, it's correct use is somewhat variable and unreliable in primary care because of factors such as those associated with child age and type of test, operator training issues, and high background noise levels confounding the results. Measures based on reported hearing difficulty (OMQ-14 questionnaire) and air conduction estimates from tympanometry have however been developed which can be also used in the analysis.[15]
- Health Utilities Index covering 4 weeks recall as used in GNOME trial and extensively validated in children.[15,44,45,46]
- 6 month study specific questionnaire on health resource use including recurrence, referral etc. Done by nurse audit of records.

In the treatment group children whose ear(s) have not got fully better at 1 month (i.e. have a residual B type in at least one ear), will be offered (a further) two months of treatment using autoinflation. All children will be asked to return at 3 months for a final screening (and to enable a full ITT analysis).

8. STATISTICS AND DATA ANALYSIS

8.1 Sample size

For a discussion on the effect size estimated from the meta-analyses please see earlier sections.[20,21] We have chosen the most conservative estimate of effect size i.e. 2.4, and think it likely that earlier presentation of cases in primary care will be associated with more serous and less mucoid effusions,[39] so easier to clear by this method. The most recent study identified by Cochrane for an updated review showed a relatively large effect.[28] The pilot also confirmed a relatively large effect from primary care OR 4, 95% CI 0.97 to 16.46. Standard power calculations using the NQuery programme have been performed based on objective tympanometric outcomes that define cure at 1 month. A 45% control cure rate at 1 month is anticipated in the calculations as found in the previous GNOME trial.[15] The best estimates are based on a meta-analysis of 4 trials that use Otovent, to be included in the update for Cochrane [22,23,28] (with one unpublished trial outcomes data, cited).[21] For cure at 1 month, the most conservative evidence based estimate of effect size is OR =2.4 Given this effect size we require 250 children (125 in each group) for a standard α=5% and power=90%. With 15% loss to follow-up, 295 are needed in total (for power=80%, 226 are needed in total). This sized sample will be able to detect a~0.3 SD difference on continuous effectiveness measures used in the study e.g. the OMQ-14 total scores, or days with hearing loss/otalgia or TADAST total score for functional hearing disability i.e. a small effect size. Differences of much less than this are not likely to be clinically significant.

8.2 Statistical Analysis

The main analysis will be an intention to treat analysis with individual children the unit of analysis rather than ears. Proportions of children cleared of one or more B type tympanograms (90% probability of effusion) at 1 month will be compared using a logistic regression model adjusting for the variables used in minimisation and other covariates as appropriate (including likely effect modifiers). Although not specifically powered to assess effect modification we will explore potentially important variables: interaction tests will be performed between randomisation groups and if statistically significant, subgroup results will be presented separately. From the GNOME trial only clinical severity was an effect modifier, however two interesting subgroups were noted on secondary analysis relating to age as a dichotomous outcome (>=6.5 years versus <6.5 years) and gender. Season and atopic status were not effect modifiers. Severity will include tympanogram readings (unilateral versus bilateral effusion), frequency of GP surgery attendance in the past 12 months for ear problems, and OMQ-14 score at baseline.

Logistic regression models will also be used for other dichotomous outcomes, and ANCOVA will be used for continuous variables adjusting for baseline differences and potential effect modifiers as appropriate. All estimates will be presented with 95%C.I.s. A trial analysis plan will be drawn up before the main trial starts.

8.3 Economic analysis

The primary analysis will take a health service perspective. The primary economic analysis will be for a 3-month follow up although the Otovent device will also be evaluated at the 1-month follow-up stage. We will measure OME associated resource use including the cost of providing the Otovent device to the treatment group and any OME related health care use in the follow up period (both groups). Healthcare use will be measured by means of GP case note review using a specially designed data collection proforma. This will be collected for all subjects and will include the three month follow up period and also a 12-month period before randomisation to test the equivalence of the study groups for resource usage. Resource use will also be collected for the 3-6 month follow up period. In addition, a parent/carer completed questionnaire will be used to obtain details of any relevant family borne costs as well as any time off work required because of the child's OME, which will enable a societal viewpoint to be taken for costs. Resource use will be costed using appropriate recent local and national cost data, including costs of health and community care,[47] prescribing costs from the BNF,[48] and NHS reference costs (DoH 2008).[49]

Two types of outcome measure will be used in the economic evaluations. Firstly, the number of children with tympanometric resolution of OME, at both 1 and 3 months post-randomisation. This will contribute to a cost-effectiveness study calculating the cost per additional child with resolved OME. The second measure will be the Health Utilities Index (HUI), using parents/carers as proxies. This will be collected at baseline 1 and 3-months, and these values will be used to estimate quality adjusted life years (QALYs) for the three month period by means of area under the curve. The incremental cost per QALY will be estimated for the Otovent group compared to the control group for a cost-utility study. The Health Utilities Index (HUI) has been widely used in children, and has been used in an evaluation of OME in children in the UK.[15]

Data will be analysed using appropriate statistical techniques such as non-parametric bootstrapping. We will investigate the effect of any differences in baseline characteristics (e.g. costs, age, gender) on results and if necessary will use regression methods to control for these. If there are problems with missing data we will use appropriate statistical techniques to impute values, for example multiple imputation. If this is used we will present results with and without imputed values. Where appropriate we will estimate incremental costs and benefits, incremental cost-effectiveness ratios (ICERs), and cost-effectiveness acceptability curves. A sensitivity analysis will be carried out to examine the effect of assumptions made in the analysis. This will include scenario analysis using the results from the trial in addition to data from other sources to model the longer term cost-effectiveness of the Otovent device. Resource use data from the 6 month audited follow up period (using a study proforma) will also be used to inform these scenario analyses.

9. QUALITY CONTROL AND QUALITY ASSURANCE

The study has been adopted by the University of Oxford's Primary Care Clinical Trials Unit, and as such will be assigned a monitor for the duration of the study. Monitoring may also be carried out by the sponsor. Regular monitoring will be performed according with the principles of ICH GCP, and data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The monitor will follow standard operating procedures to verify that the clinical trial is conducted and data are generated, documented and

reported in compliance with the protocol, ICH-GCP and the regulatory requirements. A Trial Steering Committee (TSC) and an Independent Data Monitoring Committee (DMC) will be set-up. The TSC will supervise the trial, making sure it is carried out in accordance with ICH GCP, relevant regulations and the protocol. It will agree any protocol amendments and provide advice to the investigators where necessary. The DMC will review the data and assess any safety issues.

10. PROJECT TIME TABLE

10.1 Phase 1: **Pilot study** (Thames Valley and Hampshire).

The pilot study was completed in September 2010 for the primary outcome measure, and December 2010 for 6 month outcomes.

10.2 Phase 2: Main study

The main study is planned to run over three years and requires approximately 30 active practices at any one time throughout the recruiting period, from a pool of approximately 40 study practices. A pool of practices is required as from previous experience in the GNOME study, practices/nurses left throughout the study for various reasons, therefore more needed to be recruited and trained on an annual basis. In this autoinflation study we have allowed for the loss of approximately 10 practices over the study period. For 30 active from 40 practices the recruitment rate for children randomised is 9-10 per practice or 5 children per year (see Flow diagram Appendix 1).

11. SERVICE USERS

In addition to the measures already highlighted under research governance, we will seek specific advice about improving our project protocol from INVOLVE (admin@invo.org.uk) particularly in relation to child and family experiences of primary care and impact on quality of life. A lay person will be invited to join the Trial Steering Committee to assist with the trial conduct, analysis and reporting.

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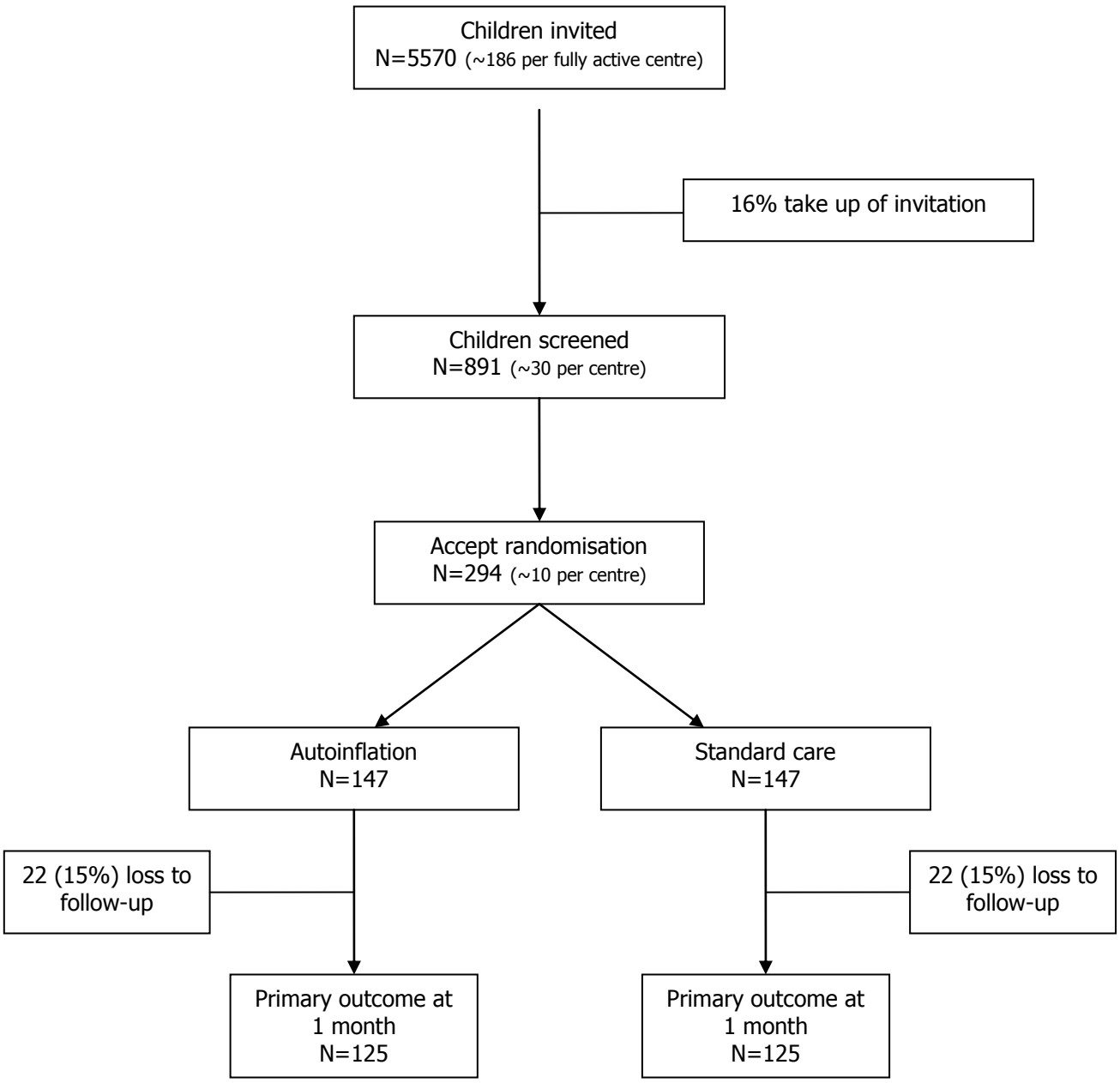
Appendix 1. Flow chart



Appendix 2. Participant flow through the study