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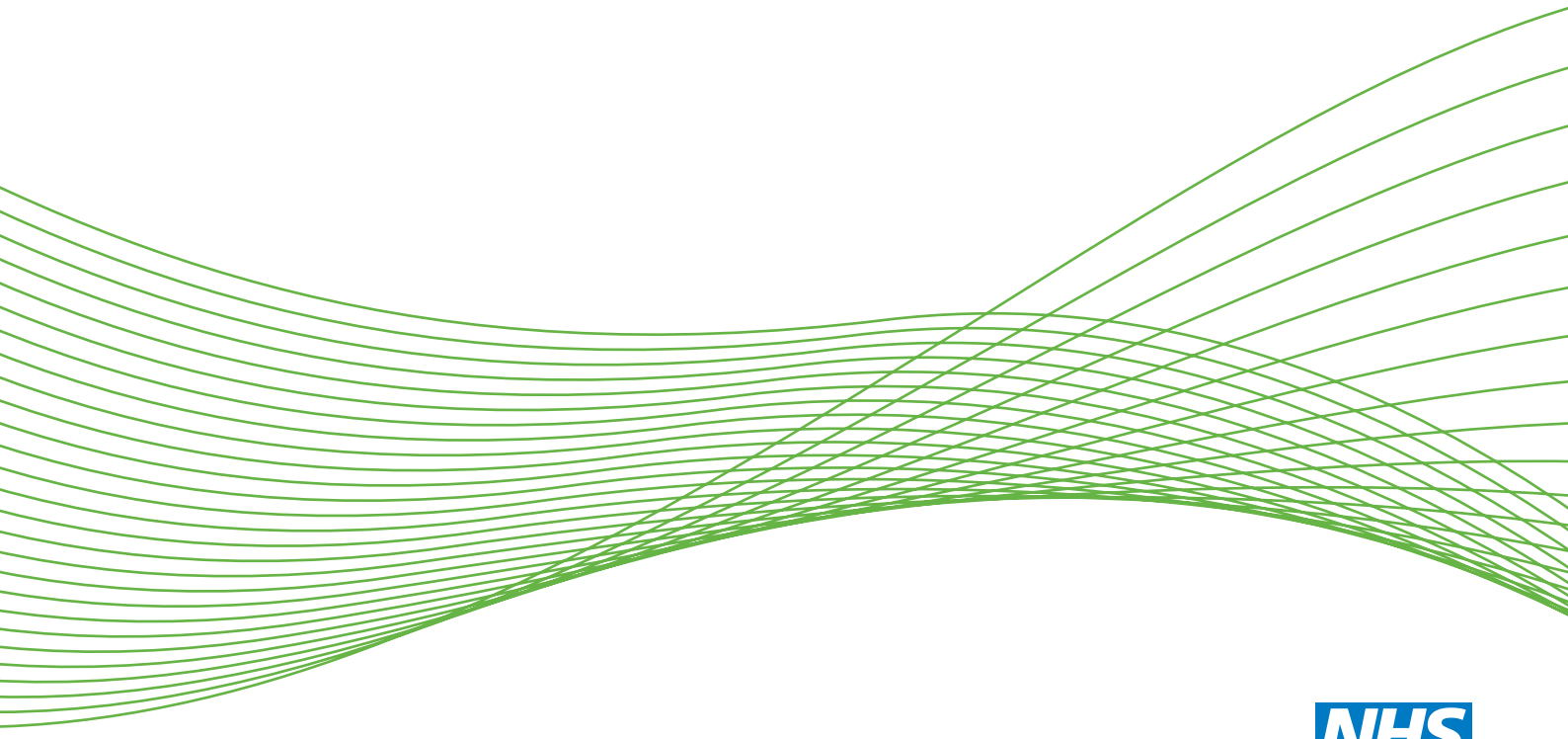

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Abstract

An open randomised study of autoinflation in 4- to 11-year-old school children with otitis media with effusion in primary care

Ian Williamson,[1]* Jane Vennik,[1] Anthony Harnden,[2] Merryn Voysey,[2] Rafael Perera,[2] Maria Breen,[2] Brendan Bradley,[2] Sadie Kelly,[2] Guiqing Yao,[3] James Raftery,[3] David Mant[2] and Paul Little[1]

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Background: Otitis media with effusion (OME) is a very common problem in primary care, but one that lacks an evidence-based non-surgical treatment.

Objective: To determine the clinical effectiveness of nasal balloon autoinflation for the treatment of OME in children.

Design: A pragmatic, two-arm, open randomised controlled trial.

Setting: Forty-three general practices from 17 UK primary care trusts recruited between January 2012 and February 2013.

Participants: School children aged 4–11 years with a history of OME symptoms or related concerns in the previous 3 months, and a type B tympanogram, diagnostic of a middle ear effusion, in one or both ears.

Intervention: Three hundred and twenty children were randomised, 160 to each group, using independent web-based computer-generated randomisation (with minimisation based on age, sex and baseline severity of OME) to either nasal balloon autoinflation performed three times per day for 1–3 months plus usual care, or usual care alone.

Main outcome measures: The proportion of children demonstrating clearance of middle ear fluid in at least one ear (with normal tympanograms) at 1 and 3 months, assessed blind to treatment. An ear-related measure of quality of life (QoL) [a 14-point questionnaire on the impact of OME (OMQ-14)], weekly diary recorded symptoms, compliance and adverse events were all secondary outcomes.

Results: At 1 month, the proportion of children with normal tympanograms was 47.3% (62/131) in those allocated to autoinflation and 35.6% (47/132) in those receiving usual care [adjusted relative risk (RR) 1.36, 95% confidence interval (CI) 0.99 to 1.88]. At 3 months, the proportions were 49.6% (62/125) and 38.3% (46/120), respectively (adjusted RR 1.37, 95% CI 1.03 to 1.83; number needed to treat = 9). The change in OMQ-14 also favoured the intervention arm (adjusted global score difference –0.42; $p = 0.001$). Reported compliance was good: 89% in the first month and 80% in months 2 and 3. Adverse events included otalgia in 4% of treated children compared with 1% in the control group. Minor nosebleeds (14% vs. 15%) and respiratory tract infections (18% vs. 13%) were noted.

Conclusion: We found the use of autoinflation in young children with OME to be feasible in primary care and effective in both clearing effusions and improving child and parent ear-related QoL and symptoms. This method has scope to be used more widely. Further research is needed for very young children, and to inform prudent use in different health settings.

Trial registration: Current Controlled Trials ISRCTN55208702.

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List of abbreviations

AIRS	AutoInflation Randomised Study
AM	active monitoring
AOM	acute otitis media
CI	confidence interval
CONSORT	Consolidated Standards Of Reporting Trials
CTU	clinical trials unit
DMEC	Data Monitoring and Ethics Committee
ENT	ear, nose and throat
GCP	good clinical practice
GNOME	General practice Nasal steroid trial of Otitis Media with Effusion trial
GP	general practitioner
HE	health economic
HTA	Health Technology Assessment
HUI	Health Utilities Index
HUI3	Health Utilities Index, version 3
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention to treat
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNT	number needed to treat
NRES	National Research Ethics Service
OM8-30	30-point questionnaire on the impact of OME
OME	otitis media with effusion (or glue ear)
OMQ-14	14-point questionnaire on the impact of OME
OR	odds ratio
PCRN	primary care research network
PCT	primary care trust
PCVC-CTU	Primary Care and Vaccines Collaborative Clinical Trials Unit
PP	per protocol
PROM	patient-reported outcome measure
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RN	research nurse
ROC	receiver operator characteristic
RR	relative risk
RTI	respiratory tract infection
SD	standard deviation
TADAST	Two Alternative Auditory Disability and Speech Reception Test
URTI	upper respiratory tract infection

Plain English summary

Otitis media with effusion is known more commonly as glue ear and is a very common condition in young school children. It is a collection of fluid behind the eardrum causing hearing loss at a time when children are developing language and social skills, and can also lead to physical ill health and poor quality of life (QoL). Although children tend to improve naturally by 3 months, some children do not and have persistent or recurrent untreatable problems, eventually requiring surgery. Autoinflation is a simple technique that increases pressure in the nose, which opens the Eustachian tubes and equalises middle ear pressures, in turn helping to clear the fluid. This study was designed to examine if regular autoinflation with a purpose-made nasal balloon alongside standard care was better than standard care alone in clearing middle ear fluid in affected children seen in primary care. To answer this question we studied 320 children aged 4–11 years with confirmed glue ear and recent or current symptoms. All children received standard care, but half ($n = 160$) performed autoinflation three times per day for up to 3 months. Children and their parents were trained to use the nasal balloon by the study nurse. We assessed the children again at 1 and 3 months and found that children using autoinflation were 36% (at 1 month) and 37% (at 3 months) more likely to show resolution of fluid than children who received standard care alone. Additionally, QoL was significantly improved in children who had performed autoinflation. The method was also found to be good value for money for the NHS over the 3-month period. Most children were able to perform the technique and comply with the treatment schedule. This study has shown that autoinflation with a nasal balloon, when used in addition to standard care, is an effective treatment for both clearing the middle ear fluid and improving the QoL of children with glue ear symptoms, and we think it should be more widely used.

Scientific summary

Background

As many as 46% of young school children develop otitis media with effusion (OME). Although most episodes resolve naturally, 10% will last 1 year or more. The problem with such a commonly seen condition is that it is often regarded as 'normal', even though the global and specific impacts can be as great in some children identified in primary care as in those subsequently undergoing surgery. These impacts include reported hearing difficulties, poor physical ear-related health, and behavioural and developmental concerns. Currently, there are no available evidence-based interventions suitable for primary care use to assist with temporising management. The recommendation to wait for natural resolution is often seen as unsatisfactory delay by families and children, with concurrent inappropriate use of antibiotics and other harmful, ineffective and undesired remedies compounding the problem. Autoinflation is a simple method that, in this study, involves inflating a balloon by blowing through the nose three times per day, with some preliminary hospital trial evidence for its effectiveness. However, trial data are preliminary and insufficient, with uncertain generalisability to the majority of affected children.

Objectives

A pilot study was performed first to assess feasibility, compliance and improve the study logistics for a primary care trial.

Main trial objectives

1. Tympanometry: the primary aim was to evaluate the clinical effectiveness of autoinflation in resolving OME at 1 and 3 months by assessing the proportions of children showing rigorously defined improvement, that is, tympanometric resolution of at least one type B tympanogram (fluid) ear per child back to normal pressures A/C1 types. Secondary tympanometric objectives evaluate resolution in individual ears at both 1 and 3 months.
2. Clinical outcomes: evaluation of the clinical effectiveness of the intervention on main OME symptoms (e.g. hearing difficulty, earache) using a diary score. A total ear problem (mapped) quality-of-life (QoL) measure using a patient-reported outcome measure [a 14-point questionnaire on the impact of OME (OMQ-14) item subset of the Medical Research Council-developed 30-point questionnaire on the impact of OME], compliance and adverse events were also measured.
3. Health economic: assessment of 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 quality-adjusted life-year (QALY). Evaluation by notes audit of the 12-month health economic (HE) outcomes.
4. Qualitative: to describe the experience of using autoinflation, including nurse-observed competence and reported compliance, and develop an easy-to-use training package for everyday practice.

Methods

The pilot study demonstrated excellent feasibility and compliance with the method in the target age group, and improved the logistics and costing for the main study.

The randomised controlled trial

Three hundred and twenty children from 43 UK practices, aged 4–11 years and attending school, and with either reported OME symptoms/concerns in the previous 3 months or relevant notes on presentation history were enrolled in the study. Children were also required to have confirmed effusion behind one or both eardrums using tympanometry (with otoscopy). Children were individually randomised using web-based randomisation with minimisation by the nurse to either the practice's usual care alone, or autoinflation three times per day for up to 3 months [where effusion(s) remained at the 1-month assessment] plus usual care. Tympanometry outcomes at 1 and 3 months were anonymised by the Primary Care and Vaccines Collaborative Clinical Trials Unit and assessed blind by an expert panel. Analysis was by intention to treat (ITT) and per protocol (PP) according to an analysis plan.

The health economics methods

The HE analyses base case took a NHS perspective for both the cost-effectiveness and the cost–utility analyses. Both analyses were based on the main clinical trial results.

The qualitative methods

Semistructured face-to-face and telephone interviews were conducted with a purposive sample of 19 practice nurses and 14 parents whose children had participated in the AutoInflation Randomised Study. The interviews were digitally audio-recorded and transcribed verbatim. NVivo 10 (QSR International, Warrington, UK) computer-assisted qualitative data analysis software was used to facilitate data management and a thematic analysis was conducted.

Results

Randomised controlled trial

Among the ITT population, 109 children experienced resolution of their B-type ears to A or C1 at 1 month, 62 (47%) children in the autoinflation group and 47 (36%) children in the standard care group. At 1 month, those in the autoinflation group were 36% more likely to have resolution of at least one B-type ear [relative risk (RR) 1.36, 95% confidence interval (CI) 0.99 to 1.88; $p = 0.0582$]. Sensitivity analyses using multiple imputations and a PP population analysis showed no significant differences between groups.

Pre-specified subgroups analyses of age (< 6.5 years vs. ≥ 6.5 years), severity (one vs. two B-type ears at baseline), OMQ-14 standardised total score (< 0 or ≥ 0) and sex were conducted on the primary outcome. In all cases no differences in treatment effects between subgroups were found. The *p*-values for the interaction term (treatment by subgroup) in the model ranged from 0.25 to 0.50.

The resolution of at least one B-type ear at 3 months was analysed in the same way as the 1-month primary end point. Out of 245 children, 108 experienced resolution of at least one B-type ear at 3 months, 62 of 125 (50%) in the treated group and 46 of 120 (38%) in the standard care group. At 3 months, those in the autoinflation group were 37% more likely to have resolution of at least one B-type ear (RR 1.37, 95% CI 1.03 to 1.83; $p = 0.0283$).

An analysis of each ear separately was conducted, adjusting for the correlation between ears from the same child using generalised estimating equations. Results were very similar to the main per-child analyses at both 1 and 3 months [RR 1.38, 95% CI 1.01 to 1.87 ($p = 0.04$); and RR 1.41, 95% CI 1.05 to 1.88 ($p = 0.02$), respectively].

At the selected 3 months end point, the adjusted mean change from baseline in the standardised OMQ-14 total scores was greater in the autoinflation arm than in the routine care arm. The difference between groups was –0.42 points (95% CI –0.63 to –0.22 points). This score difference represents an adjusted effect size of 0.48 (of a standard deviation; $p \leq 0.0001$), favouring intervention.

Symptom diary days during which parents reported that their child had hearing loss, earache, sleep disturbance, problems concentrating, as well as days on which pain relief was required and days off school, were summarised in accordance with the statistics plan (to avoid multiple outcomes) as days with any problem. Overall, children in the autoinflation arm had had fewer days with any symptom/problem at 1 month [odds ratio (OR) 0.66, 95% CI 0.41 to 1.05; $p = 0.08$] and at 3 months (OR 0.58, 95% CI 0.37 to 0.90; $p = 0.02$).

With regard to compliance with the method, 116 out of 130 (89%) parents reported using autoinflation 'most' or 'all of the time' during the first month of treatment, consistent with the daily compliance charts. This level of compliance appears to have been maintained in those continuing treatment up to 3 months (68/85, 80%).

There was very little difference between treatment arms in terms of numbers of children with a nosebleed (15% vs. 14%), but there were more reported respiratory tract infections (RTIs) in the treated group (18% vs. 13% of children, $n = 37$ vs. $n = 18$ episodes). Most of the RTIs were classified, however, as mild afebrile rhinorrhoea. Eight children in the autoinflation arm (compared with two in the routine care arm) reported otalgia. One child in the autoinflation arm was hospitalised with mild/early mastoiditis that was considered by the Data Monitoring and Ethics Committee review to be non-attributable to the method and made a full recovery .

A meta-analysis of similar trials, identified in the most recent Cochrane systematic review, with outcomes at 1 month (ear-based analysis B to A/C1) favoured autoinflation (RR 1.61, 95% CI 1.26 to 2.06). When the pilot study was combined with the main study as per the statistical plan, the combined RR of the two primary care setting studies was 1.37 (95% CI 1.00 to 1.87).

Health economic evaluation

The cost-effectiveness analysis based on the statistically significant difference in cases resolved puts the cost per case resolved at £132. Although the cost difference was not statistically significant, it was based almost entirely on the cost of the intervention.

The cost per QALY analysis showed the use of the Otovent device (ABIGO Medical, Askim, Sweden) to be just likely to be a cost-effective intervention. The uncertainty reflects the small and non-statistically significant difference in QALYs, a generic rather than condition-specific measure of outcome.

Qualitative study

Three key themes emerged from the analyses that were interpreted as relevant to the research question.

Rationalising

The first point of contact for parents with concerns about their child's hearing is usually the general practitioner. Parents generally expressed a desire to take action, and a waiting period was often seen as an unacceptable delay. Access to good-quality information and advice helps parents to rationalise decisions and make informed choices for their children.

Primary care management

Nurses were sufficiently informed and skilled in screening children with tympanometry, and were seen by families as accessible and competent to fulfil this role. The collaborative relationship between the nurse, parent and child was important for co-operation with tympanometric screening and training in the use of the nasal balloon. Demonstration of autoinflation by the nurses and/or parents helped the children to master the technique.

Engaging with monitoring and treatment

Autoinflation was reported as acceptable to families. Adherence over a period of 1 month was achievable for most parents. Some children reported initial anxieties, but this was overcome with support and encouragement. Adopting the technique as part of the child's normal routine (e.g. when cleaning teeth or using asthma inhalers) may be important for the longer-term use up to 3 months.

The nested qualitative study highlights the potential for an improved and more proactive role of general practice in the early diagnosis and treatment of this common childhood condition.

Conclusions

Our main findings reveal that autoinflation using the balloon method is both feasible and cost-effective in a primary care setting. A number needed to treat of 9 at both 1 and 3 months was found for improved clearance of middle ear effusions, beyond natural resolution effects alone (usual care). The symptom diaries (describing hearing loss, earache, etc.) showed significant and encouraging improvements by 3 months, the recommended waiting time, as did the mapped ear-related QoL measure (OMQ-14). Although the sample is of good generalisability, children younger than 4 years may perform the method less reliably, and it does require commitment to a regular treatment plan over 1–3 months.

In terms of capacity to change clinical practice, we have demonstrated that this method is clinically effective, good value and safe and acts in a timely fashion for the majority of children likely to be treated in the NHS with symptomatic OME. It should, therefore, be an attractive initial stage option when one considers the unsatisfactory nature of present limited temporising options, which include doing nothing, giving a 'known' ineffective and harmful treatment such as antibiotics or a decongestant, and referring cases on for further evaluation for surgery (which is used to treat a minority, usually those who have experienced unacceptable delays).

From a clinical perspective, the vast majority of children with a working diagnosis of OME will be eligible for a form of empirical management – the modus vivendi of general practice. Thus, although there are inevitable limits to what one can conclude from a large, open pragmatic trial such as this, the sum of the new evidence appears sufficiently strong to justify much wider use of autoinflation than is the case at present.

Suggestions for further research

Implementation and support aspects are needed to improve and refine recognition, diagnosis and impact of OME in primary care settings. This may include a web-based support intervention to promote self-efficacy and support the wider use of the nasal balloon in primary care. This could be supplemented with the further development of near-patient hearing tests and/or short-form questionnaires of impact as developed by the Medical Research Council. Development of clearer self-management plans for OME should be updated, as for asthma, in relation to best use of autoinflation. This requires further pragmatic research including HE evaluation, systematic and consensus review.

Different autoinflation methods may be compared in terms of age-related feasibility, and trials are needed of its effectiveness as a recurrent or second-line treatment in primary and secondary care settings.

The different forms of the Politzerization method that include nasal balloon autoinflation may be a productive area for new treatments. Modified devices may lend themselves to drug delivery systems that better reach the Eustachian tubes than topical nasal sprays.

Trial registration

The trial is registered as ISRCTN55208702.

Funding

Funding for this study was provided by the Heath Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Definition

The term otitis media with effusion (OME) is often used synonymously with 'glue ear'.[1] The descriptive definition is based on the intraoperative findings of sticky mucinous secretions behind the eardrum that can hamper the free movement of the ossicles in the middle ear. The viscosity of the middle ear fluid has been found to vary and the fluid is sometimes described as serous or secretory.[1,2] Effusions are associated with notional conductive hearing losses of about 15–45 dB owing to damping effects on sound transmission to the inner ear. OME occurs usually in one ear, but frequently in both ears.[3] Probably the earliest and most relevant description of the condition from a primary care perspective was made by Dr John Fry, who wrote about the 'catarrhal child': a syndrome of coughs, colds, catarrh and subhealth, in which OME and frequent or persistent upper respiratory infections are the predominant features, and which presents most commonly in young children of early school age.[4]

Natural history and scale of the problem

As many as 80% of children of all ages develop OME.[3] Most such episodes are anticipated to resolve naturally, with an average duration of 6–10 weeks, and with just 10% of episodes lasting ≥ 1 year.[5,6] The problem with such a common condition is that it is often regarded as normal. The prevalence rises to 46% (a secondary peak) in the early school years,[6] when recurrent ear-related symptoms and broader developmental concerns most often bring the condition to light,[7,8] and not infrequently results in surgical referral for grommets.[1,9,10] Time to resolution of effusions remains clinically unpredictable; many last ≥ 3 months and 30% are recurrent.[3,11] In the UK, about 200,000 children are seen every year with this problem in primary and community care.[1,12] The full scale of the total health burden is only partly reflected in high international rates for grommet surgery,[13–15] but with falling rates observed in the UK.[16] In the USA, in 2004, as many as 2.2 million people were diagnosed, at an estimated cost of US$4B.[17]

The impact of this very common condition on child physical health, hearing, speech, behaviour, development and mapped quality of life (QoL) has been found to be just as great in a primary care sample as in hospital samples.[9,18–21]

Clinical management

Diagnostic evaluation in primary care

Initial temporising management in primary care is often pragmatic, ad hoc and influenced mainly by parental concerns.[1,4] Research about diagnosis of OME suggests that more could be done in this setting to improve diagnostic accuracy.[22–25]

Although the history alone has moderate specificity, it is not particularly sensitive for how a child is likely to function, for example in a noisy learning environment.[26,27] OME has been described as a chronic 'invisible' illness that can be relapsing and frustrating for both the parent and child. It has been clinically noted that uncertainties are often expressed by families regarding whether the root cause is a behavioural issue or a genuine hearing problem. Concerns about school achievement have also been suggested as an important driver for surgical intervention.[28] Case ascertainment for treatment poses several dilemmas, caused not just by (a) the current lack of available 'proportionate and cost-effective' treatments (see *The evidence for non-surgical interventions*), but also by (b) lack of agreement within the profession about what one is treating: whether a disease or condition, a disorder, a disability or a global qualitative impact, as one moves

from the more biomedical to a patient-centred model of the condition.[19,29] In general practice, evaluating this multidimensional aspect of OME appears to approximate to a simple formula or rule of thumb as: history of **persistence** (reported duration) × perceived **severity** (number of related surgery attendances and/or level of concern about salient markers in different domains, e.g. hearing-/speech-/ear-related physical health/behaviour and development). Symptoms and concerns are reasonable but variable predictors of the state of the child's ears in terms of current effusion status,[30] reinforcing the case for improving clinical assessment in primary care both at the point of treatment and to improve accuracy of referrals.

A careful clinical history is of central importance for case recognition and appears reasonably good for purpose; UK ear, nose and throat (ENT) referrals, although variable, are fairly conservative: about 15% referred in the General practice Nasal steroid trial of Otitis Media with Effusion (GNOME) trial, and with ≈50% of children nationally who are referred on, but who are subsequently found not to meet the strict criteria for grommets (after a period of waiting conducted in hospital, which will necessarily include natural resolution effects).[9,10,30,31] The majority of all affected children will initially undergo observation in primary care or in the community.[1] The more frequently that parents report ear-related episodes in their child in the previous 12 months, the greater the predictive values for the finding of an effusion on screening tympanometry [two or more episodes have an odds ratio (OR) of 2.9, and five or more have an OR of 4.3].[32] However, it is probable that children with OME-related impacts remain under-recognised.[33] The intermittent history is problematic, and the spectrum of need is wide.[1,34] In this context, the current markedly limited range of evidence-based treatments both on offer and capable of informing policy requires strengthening.

A detailed history, for example finding evidence of reported hearing difficulty with other typical symptoms/concerns associated with OME, may be supplemented by good-quality otoscopy (using a halogen light) or, better still, by using tympanometry.[1] There are no studies of symptom predictors of effusions from primary care, but the sensitivity of history is thought to be around 70%.[1] Both otoscopy and tympanometry are more objective measures in pinpointing the current status of effusion(s) than parent report alone, and have some potential to improve case recognition and clarify those requiring treatment. Tuning fork tests are unfortunately unreliable for the vast majority of children when age at presentation is considered. Relevant audiological tests that improve precision include free-field voice testing done by specialists, and this is probably the most reliable evaluation of hearing for the presenting age group.[1] Accurate pure-tone audiography is not really feasible and is seldom valid in primary care settings.

However, all currently used tests and assessments, irrespective of setting, remain only weakly predictive of the QoL experienced by children and their families.[21] Patient-reported outcome measures (PROMs) can capture such information and are relatively new for the condition of OME. They are moving from the research to clinical audit stage in secondary care, but remain at the research stage in primary care.[9,18,29] Such outcomes are intrinsically holistic and both child and family centred, and thus well suited to primary care use in their shortest available pragmatic form(s). They are endorsed as an important part of the battery of assessments by Cochrane, and are also seen to be of high priority by other experts.[35]

Prognosis

Prognostic factors for likely persistence have been extensively reviewed, and nearly all have ORs below 2, curtailing their usefulness somewhat in clinical settings.[31,32,36] Age appears to be the best available predictor of population outcome, with fewer children aged > 6–7 years 'troubled' by OME. There is also a clear effect of season, with fewer cases found in the summer months (some of these may be allergy rather than infection related).[3,31,32]

Birthweight and skull size have been mooted to have prognostic relevance as have genetic factors,[8,31] but such variables have not found any clinical application. There appears to be little, if any, effect of sex at the level of disease/condition, although it is known that boys are slower to read than girls, and so sex may be a confounding factor in presentation and by contributing to outcome severity. This illustrates the importance of cofactors that may either heighten (or reduce) the impact of the OME, such as poor communicating styles at home or school, or reduced ability to lip read because of uncorrected poor visual acuities.[37]

Sharing age-related natural history-based prognosis with families is very important, but generally it is difficult on the individual level to predict which children will persist with effusions for 3 months, thus partly justifying a watch-and-wait period.

The evidence for non-surgical interventions (available for use in primary care)

Published systematic reviews have evaluated many studies across a wide selection of non-surgical interventions that are currently used in the treatment of OME. The selected interventions considered here have been made with multidisciplinary input from (a) the current *British Medical Journal* Clinical Evidence team;[34] (b) ENT colleagues editing the Scott-Brown *Otolaryngology* series;[31] and (c) the National Institute for Health and Care Excellence (NICE)'s 2009 grommets review.[1] The original (trial protocol) searches were based on a MEDLINE search from 1966 to March 2010, EMBASE from 1980 to March 2010, and the Cochrane Database of Systematic Reviews from inception to 2010. All searches have since been updated using MEDLINE and EMBASE for systematic reviews to include individual randomised controlled trials (RCTs), and all publications using the key terms 'otitis media' and/or 'OME' that have been published between January 2006 up to August 2014. The main interventions of interest and summarised below are antibiotics, steroids, antihistamines/decongestants and autoinflation. Cochrane has underlined the importance of OME as a condition of considerable importance, with nine current published reviews on the topic and one protocol on its website (www.cochrane.org), with several of these reviews updated over the study period.

The evidence for antibiotics

The most recent updated Cochrane review suggests that antibiotics are unlikely to be beneficial. The research was extensive and included 23 trials and 3027 subjects.[38] The author's main conclusion was that there is no statistically significant evidence that antibiotics produce resolution of OME in the short term. Six studies[39–44] ($n = 738$ children) were combined and show slight benefit of long-term antibiotics at 6 months, but none of these was from primary care. Unwanted effects of antibiotics reported in the literature include rashes, nausea, vomiting, diarrhoea and anaphylaxis. Unnecessary use of antibiotics also promotes the development of antibiotic resistance and the medicalisation of minor illness.[45–50] A few uncertainties remain for targeted, well-considered and selective use of antibiotics.[46] Speculatively, this may include secondary care subgroups as an alternative to surgery, or for any antibiotic-sensitive biofilm infection, or where recurrent acute otitis media (AOM) rather than OME is deemed to be the predominant underlying pathology.[51]

To conclude, with inadequate evidence for routine use of antibiotics from primary care, a number needed to treat (NNT) was estimated to be over 20,[52] and with the escalating level of threat from antibiotic resistance, antibiotics should not be recommended for routine use.

The evidence for steroids

A Cochrane systematic review,[53] search date August 2010, which included 12 studies and 945 patients, found some evidence for improved short-term resolution of OME in those treated in secondary care with oral steroids, either alone or combined with antibiotics. However, there is insufficient evidence to date to determine their effect on resolution of OME-related symptoms or on longer-term outcomes. The systematic review also included several trials, and a UK primary care study of topical intranasal corticosteroids, and concluded that there was sufficient evidence to make the statement that there was 'no benefit from topical intranasal steroids'.[18,53] Oral steroids have, however, been mooted as a simple, cheap treatment with the advantage that they could be used for a wide age range of selected affected children. However, better evidence of their effectiveness in clearing effusions, in improving patient-centred outcomes in the short and longer term, evidence for their cost-effectiveness and, importantly, a comprehensive evaluation of any associated harms is still required. There are concerns from both parents and professionals about the appropriateness and safety of courses of oral steroids for very young children in this clinical context, that is, a chronic intermittent condition of variable severity that eventually self-limits. These important issues and desired outcomes are being addressed in an ongoing trial funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 11/01/26), with selected patients being recruited from hospital settings.

The 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.[35,54] In total, seven clinical trials were found suitable to be included in Cochrane.[55–61] Subsequently, a literature search (search date November 2013), which is an update of the original Cochrane systematic review, was performed using the standard Cochrane search method, as described in full elswehere.[35] Two additional references to clinical trials were found, one of which was a completed RCT carried out on a total sample of 40 children.[62] Different methods of autoinflation using Valsalva manoeuvre techniques, party blowers and face masks, as well as purpose-manufactured devices, were considered in both meta-analyses. The nasal balloon technique using Otovent (ABIGO Medical, Askim, Sweden), which was developed by Professor Stangerup (see *Chapter 3*, *Trial intervention* for a full description), and essentially consists in inflating a purpose-manufactured balloon through the nose, and the EarPopper® (Micromedics, St Paul, MN, USA) (a device operating to give a steady flow of air to the nose, which needs to be co-ordinated with the act of swallowing, which opens up the Eustachian tubes) are the only two purpose-manufactured standardised delivery devices, and appear also to yield the most promising results so far in terms of beneficial ORs.[35] Four small studies[54–56,62] (one unpublished except in a review) that used the balloon intervention (Otovent) as the method for autoinflation were the basis of our power calculation. Combining these trials gives a potentially homogeneous total of 336 children and is completely dominated by secondary care studies. For the tympanometric outcomes at 1 month, the OR based on all four relevant studies was 2.4, but was not significant. The Cochrane authors, although finding a large aggregate effect size for the autoinflation method with a relative risk (RR) of improvement of 2.47 for tympanometric outcomes, reported wide confidence intervals (CIs) going through 1 (95% CI 0.93 to 6.8). The authors recognised that evidence to recommend widespread use of autoinflation in general practice was missing (a view echoed in subsequent NICE guidance),[1] and highlighted the need for a large-scale pragmatic trial in primary care with a longer follow-up term of > 1 month.[35]

The most recent updated MEDLINE search in August 2014 revealed one further autoinflation study.[63] This small pilot study involved a modified face mask with an external counter-pressure system intended for use in very young children. One must conclude that the clinical efficacy and effectiveness of autoinflation in a primary care population remains completely untested and requires full evaluation before wide-scale 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 and in the community, and it is increasingly clear that there are, as yet, no evidence-based treatments that work in this setting.[1,31,34,35,52,53] Lack of a good non-surgical intervention is arguably a major factor fuelling the substantial rates of inappropriate early referral for consideration of surgery, which is thus far the only proven effective treatment.[16,37]

There are no known or reported harms associated with nasal autoinflation to date, with higher respiratory tract infection (RTI) rates (including AOM) noted in the control groups in two studies, making it unlikely that the increased pressure in the nose during autoinflation can spread infections, or that it acts as an object that produces cross-infection.[55,56] Patent details outline advantages of controlled air flow and non-damaging pressures inside the nose (the latest patent was filed in September 2008, patent reference US 20100071707A1).

Perhaps compliance is the major potential weakness with this technique,[31] and it can probably reliably be performed only in school-aged children (4–5 years and older). Nasal balloon autoinflation using Otovent (≈£5) has the advantage of being considerably less costly than using the EarPopper (≈US$200). Otovent also has better preliminary evidence than the single manufacturer randomised study of just 94 children for the EarPopper,[57] thus making the nasal balloon method the intervention of choice for further evaluation.

In summary, the current best, but very limited, evidence from three small homogeneous moderate-quality studies combined at 1 month in the Cochrane review[35] suggests there may be a higher rate of short-term tympanometric resolution in children using a purpose-manufactured balloon device (Otovent) than in control subjects.[55,56,61] All the meta-analysed studies, however, failed to provide a definitive answer; many lacked intermediate follow-up and all lacked any long-term follow-up. The Cochrane 3-month meta-analysis,

although reporting statistically significant results, used combined (audiometric and tympanometric) outcomes. Furthermore, no relevant important patient-centred outcomes were included in the review, and all identified studies were conducted entirely in highly selected secondary care/specialist populations.

The evidence for other interventions

A *British Medical Journal* clinical evidence review[34] found that mucolytics are unlikely to be beneficial, and that antihistamines and/or oral decongestants are likely to be ineffective and have unwanted side effects.[64] Hearing aids have not as yet been properly evaluated, with no good comparator studies available.[1]

The evidence for surgery

For the sake of completeness, and context, a brief synopsis of the evidence for surgery is included here to help bring out some of the issues with current management. Surgery is demonstrably and clearly effective for a carefully selected minority of children, that is those with more severe histories and/or intractable presentations.[1,37] OME/glue ear remains consistently one of the commonest reasons for childhood surgery (inserting grommets/removing adenoids).[15–17,65]

However, surgery is known to have a number of significant disadvantages, ranging from high costs and child-and-family preference for a non-surgical option to risks from anaesthetic (with post-operative adverse events that include otorrhoea,[66] perforation, tympanosclerosis, residual hearing loss[1,14,31] and significant re-insertion rates[8]). But arguably the most significant limitation of surgery is that, although effective, it is a treatment that is selectively applied post hoc, allowing many children to remain disadvantaged by their hearing loss and other clinically and socially significant OME impacts over a wait of approximately 9 months, rather than in a more timely fashion. This observation has been labelled the *treatment paradox*.

Conclusion

Temporising medical management is frequently given in general practice, and often includes prescribing antibiotics, decongestants and antihistamines, all of which have been shown to be clinically ineffective, and, worse still, have significant harms.[1,12,34,38,64] Furthermore, these interventions are associated with substantial NHS costs. Antibiotic prescription in primary care is rising progressively again, and has now exceeded the peak in the late 1990s, further driving the development of antibiotic resistance, which may lead to serious infections becoming untreatable.[47,50] The high prevalence of OME, and the fact that it is estimated that one-third of all cases of otitis media are primarily OME related,[2,12] means that estimated rates of 80% antibiotic prescribing for all types of otitis media episodes in primary care are potentially reducible by a further 20–30%.[12] Finding an appropriate, feasible and low-cost management option for primary care for the majority of affected children must therefore be seen as an urgent priority, with the status quo of 'watch and wait' sometimes interpreted by parents as 'doing nothing' or as a form of demand suppression.[67]

Autoinflation has been identified by a systematic search through the evidence as the best potential option for primary care. If found to be the case from research, a low-cost, safe and clinically effective treatment might resolve effusions and related symptoms, concerns and global impact on the child's life and development. There is thus potential to improve child and parent QoL, increase satisfaction and adherence to a recommended watch-and-wait strategy, and also to reduce the harms of overprescribing antibiotics and other presently misapplied treatments.

A simple autoinflation method (Otovent) used for 1–3 months is proposed here in a pragmatic, open, randomised two-arm controlled trial in UK primary care, in which both arms receive usual (routine or standard) management, in order, primarily, to evaluate both clinical effectiveness and cost-effectiveness of the intervention. Health economic outcomes are proposed to be collected up to 12 months post randomisation.

Primary aim and objectives

The primary aim of the study is to evaluate the clinical effectiveness of autoinflation in resolving OME at 1 and 3 months by assessing the proportions of children showing rigorously defined improvement as accepted by Cochrane, that is, tympanometric resolution in at least one ear per child of a type B tympanogram (fluid) to normal, type A/C1, tympanograms.[35]

Secondary aims and objectives

1. Tympanometric: assessment of the proportions of ears showing resolution from B to A/C1 types at 1 and 3 months.[35]
2. Clinical outcomes: evaluation of the clinical effectiveness of the intervention on total symptoms (e.g. hearing difficulty, earache and difficulty concentrating) using a total diary score. We also used a total ear problem (mapped) QoL measure using a PROM [a 14-point questionnaire on the impact of OME (OMQ-14), which is a subset of the Medical Research Council-developed 30-point questionnaire on the impact of OME (OM8-30)].
3. Health economic (HE) assessment of 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 quality-adjusted life-year (QALY). Evaluation by notes audit[30] of the 12-month HE outcomes.
4. Qualitative: to describe the experience of using autoinflation, including nurse-observed competence and reported compliance, and develop an easy-to-use training package for everyday practice.

Chapter 2 Pilot study

Introduction

A pilot study was proposed in advance of a main trial of autoinflation to test the feasibility of recruitment rates, randomisation procedures, training of practice staff, acceptability to patients and compliance with the autoinflation device. The pilot also improved costing estimates for the main trial.

Methods

Aims and objectives

The principal aims of the pilot study were to test the feasibility of conducting a trial of autoinflation in a primary care setting and, in particular, to evaluate children's compliance in using the device. Other benefits of piloting are as indicated above.[68]

Setting

The pilot study was set in four general practitioner (GP) practices recruited through the Primary Care Research Network (PCRN) (in Hampshire, Wiltshire, Buckinghamshire and West Berkshire).

Ethics approval and research governance

Ethics approval for the pilot and main study was awarded by the National Research Ethics Service (NRES) on 10 August 2009, reference number 09/H0504/75 (see *Appendix 1*). Research governance approval was obtained from four primary care trusts (PCTs) (in Hampshire, Wiltshire, Buckinghamshire and West Berkshire).

Recruitment of practices and research nurses

Four practices participated in the study. All nurses had current good clinical practice (GCP) training and attended a structured study training day held at their practices and delivered by the research team. On-site training of the nurses included identifying and inviting potential participants, informed consent process, performing each assessment and use of the specific study equipment (otoscope, tympanometer and autoinflation device). In addition, a prototype study manual was given to each research nurse (RN) for reference purposes, and provided preliminary support.

Recruitment of children

School-aged children (aged 4–11 years) were identified for the study either by initial computer searches or by opportunistic case finding within the practices. Children were eligible for inclusion if they displayed symptoms typical of OME in the previous 3 months or their notes recorded a history of ear problems in the previous 12 months or a relevant presenting problem. Full details are presented in *Chapter 3*, *Recruitment of children*. The youngest children (aged 4–6 years) attending school were deemed to have highest base level of risk for OME, so were selected for screening provided they had recent symptoms irrespective of notes history.

Eligibility and informed consent

Children were assessed for eligibility according to the criteria in *Box 1*. Prior to tympanometry, all parents gave written, informed consent for screening and children were also invited to give written assent wherever deemed applicable by the RN.

BOX 1 Inclusion/exclusion criteria for the pilot study

Inclusion criteria

1. Children aged 4–11 years and attending school.
2. At least one ear with a type B tympanogram (using the modified Jerger classification).[69–71]

PLUS

3. (a) For children (aged 4–6 years) identified from the practice age/sex register, parental concern with report of at least one relevant symptom/concern associated with OME in the *previous 3 months* from the following symptom/concern checklist:[1,2,8,30,72]

    - a prolonged or bad cold, cough or chest infection
    - an earache
    - appears to mishearing what is said
    - hearing loss has been suspected by anyone
    - says 'eh what?' or 'pardon' a lot
    - needs the television turned up
    - may be irritable or withdrawn
    - appears to be lip reading
    - not doing so well at school as you or the teacher think, e.g. with reading
    - has noises in the ear or is dizzy
    - snores, blocked nose or poor sleep
    - speech seems behind other children's
    - any suspected ear problem.

OR

3. (b) For children identified in the targeted attendance screen (aged 7–11 years), a history of recent and/or recurrent otitis media or OME in the *previous 12 months* recorded in the child's medical records OR ear-related problems in the previous year including suspected hearing loss, snoring, concerns about child's behaviour, speech or educational development.[30]

OR

3. (c) For children newly presenting, relevant expressed clinical concern from the health team about OME as a cause.[30]

Exclusion criteria

1. Children with a grommet already in the eardrum, or who have been referred or listed for ear surgery.
2. Children with a latex allergy (owing to use of latex nasal balloons).
3. Children with uncommon conditions and syndromes at high risk of recurrent disease including cleft palate, Down syndrome, Kartagener syndrome, primary ciliary dyskinesia and immunodeficiency states for whom early referral is indicated.

Randomisation and concealment of allocation

Eligible children were individually randomised to autoinflation plus routine care or routine care alone via a telephone dial-in service to the Primary Care and Vaccines Collaborative Clinical Trials Unit (PCVC-CTU) at the University of Oxford.

The randomisation method used an algorithm with minimisation based on three previously found key variables: age, sex and baseline severity of OME.[18,30] Owing to the nature of the intervention use of placebo was not possible, and therefore nurses, children and families were unable to be masked to treatment allocation.

Intervention

The intervention in the pilot involved the autoinflation method using a nasal balloon (Otovent) three times per day through each nostril for 1–3 months plus routine care compared with routine care alone.

Assessments

The primary outcomes assessed were tympanometric, resolution of type B (effusions) at 1 and 3 months. Tympanometric outcomes were assessed blind to intervention group by the chief investigator.

Compliance with the autoinflation device over the study period was recorded using a daily sticker reward chart completed by the child and was also parent reported (as use of autoinflation on a 4-point Likert scale and number of times per day). The ear-related QoL questionnaire (OM8-30) and Health Utilities Index (HUI) were also evaluated in the pilot study (*Figure 1*).[30]

Results

Patient recruitment

Practices commenced their computer searches in November 2009, with 357 children invited for screening from four practices between January 2010 and May 2010. Fifty-eight children were consequently screened for eligibility and 21 were randomised into the pilot.

The pilot Consolidated Standards of Reporting Trials (CONSORT) diagram, illustrated in *Figure 2*, details the numbers of children that progressed or otherwise through the study. Two children had to be excluded after randomisation, both in the autoinflation group, one because of an existing perforation of the eardrum and the second because of a tympanometric misclassification error, leaving 19 patients who were correctly randomised into the pilot.

The baseline characteristics of children screened for the study are presented in *Table 1* and all correctly randomised children are presented in *Table 2*.

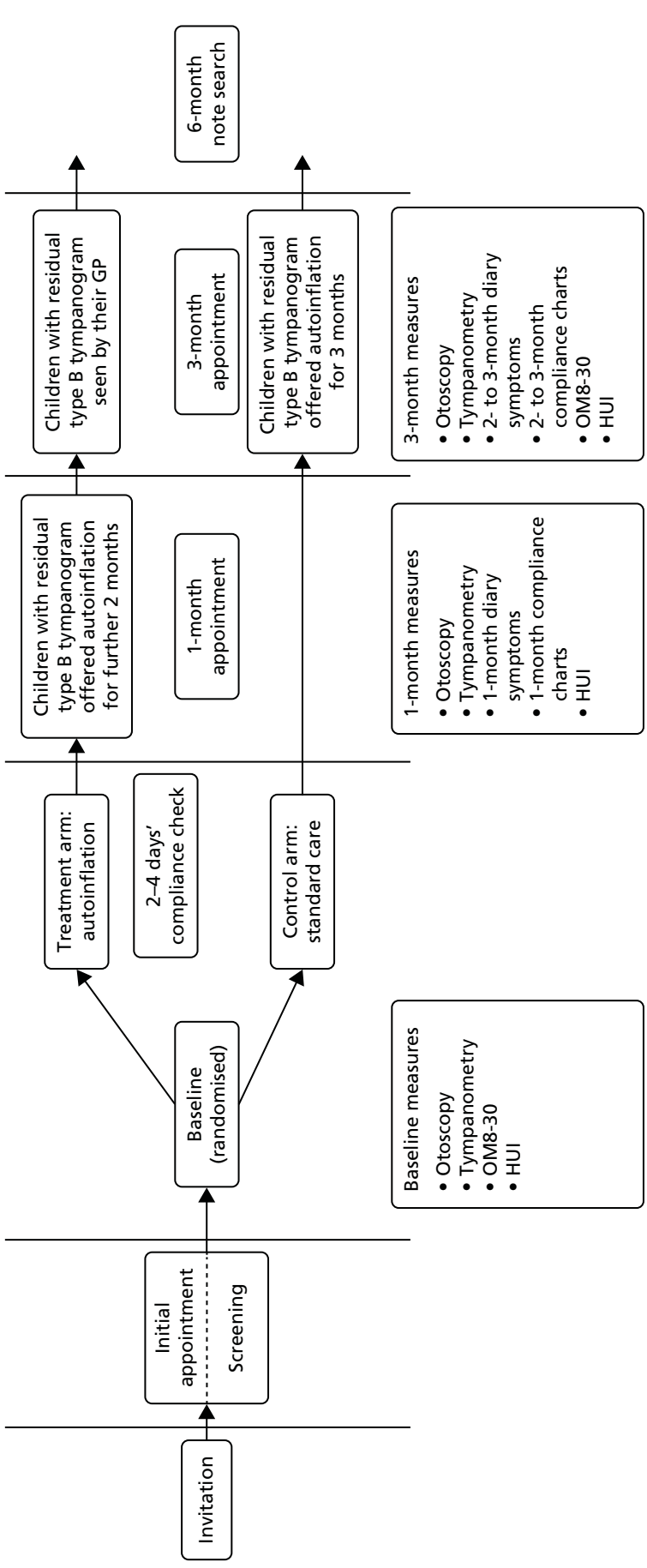

FIGURE 1 Flow of participants through the pilot study.

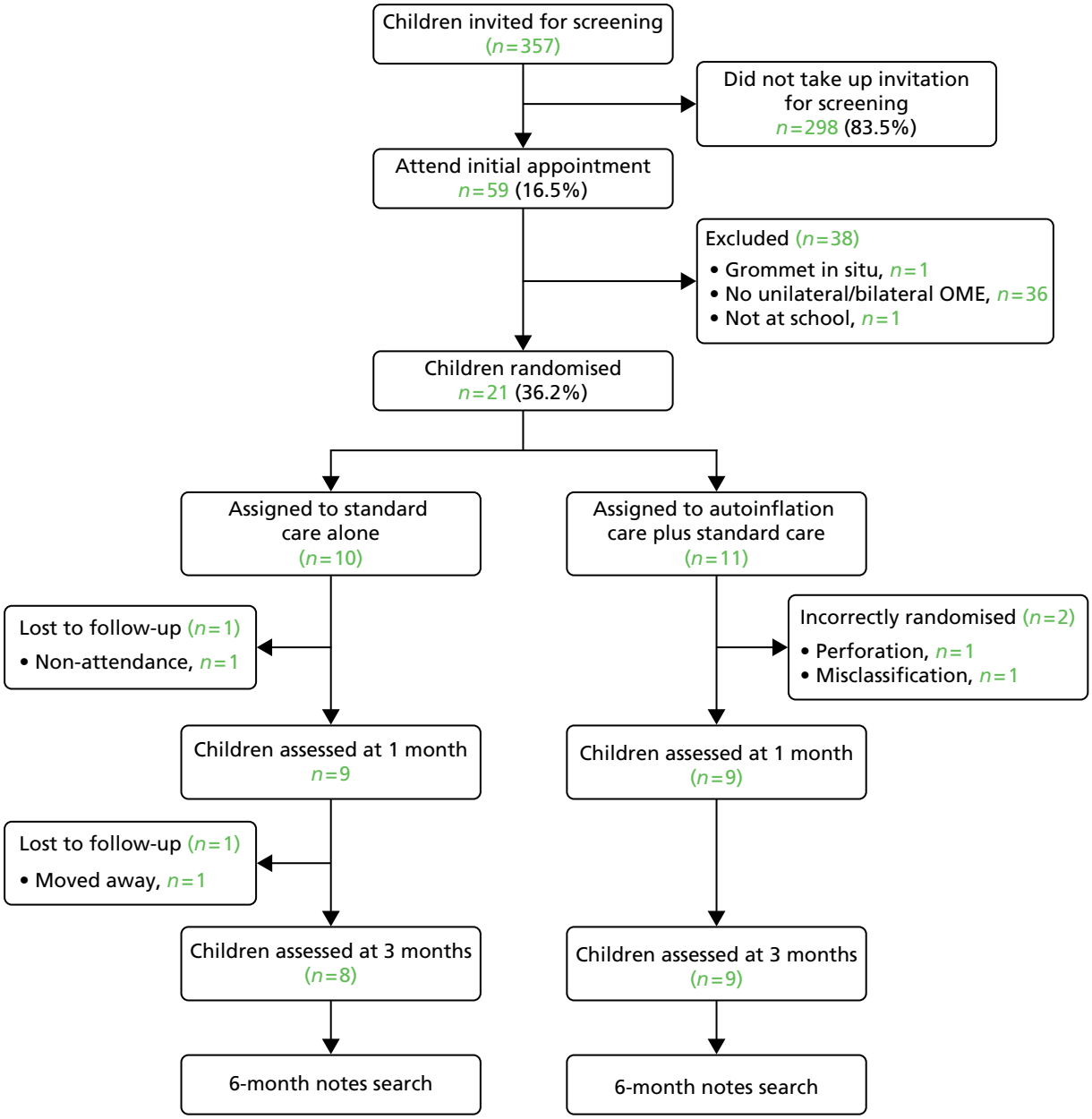

FIGURE 2 The pilot CONSORT diagram.

TABLE 1 Characteristics of screened children ($n = 58$)

Variable	*n* (%)
Age at screening (years)	
4–5	12 (21)
5–6	32 (55)
6–7	4 (7)
7–11	10 (17)
Sex	
Male	30 (52)
Female	28 (48)

TABLE 2 Baseline characteristics of randomised children

Variable	Autoinflation ($n = 9$), *n* (%)	Standard care ($n = 10$), *n* (%)
Sex		
Female	5 (56)	5 (50)
Male	4 (44)	5 (50)
Age (years)		
4–5	3 (33)	2 (20)
5–6	4 (45)	8 (80)
6–7	–	–
7–11	2 (22)	–
Ethnicity		
White	8 (89)	9 (90)
Oriental	–	–
Afro-Caribbean	–	–
Bangladeshi/Indian	–	1 (10)
Mixed	–	–
Other	1 (11)	–

Outcome measures

Objective resolution was defined by ear as change from at least one type B (fluid) to A/C1 (clear) tympanogram. Intermediate negative-pressure C2 tympanograms were considered insufficient evidence of clearance of fluid.

The main effects of autoinflation were estimated using the difference in proportions of children with fluid resolved between the two treatment arms at both 1 and 3 months.

The estimated difference between groups at 1 month based on the by-child results from *Table 3* is 11.1% (95% CI –36.0% to 58.2%), which is equivalent to an OR of 1.75 (95% CI 0.20 to 14.20).

The estimated difference at 3 months is 12.7% (95% CI –44.6% to 70.0%), which is equivalent to an OR of 1.7 (95% CI 0.2 to 12.2). This is comparable to the effect found in the meta-analysis from the Cochrane systematic review[35] for full resolution (an OR of 2.4). The power calculation estimates for the main study were considered not to require revision by our statistician.

Compliance and use of the autoinflation device

Reported compliance was very high and consistent across both reward charts and parent-reported usage (*Table 4*). However, prospective use of a reward sticker chart was considered to be the most reliable method.

TABLE 3 Summary of tympanometric resolution at 1 and 3 months

		1 month		3 months	
Severity	Resolution	Autoinflation	Standard care	Autoinflation	Standard care
Bilateral	Both ears resolved	1	0	1	0
	One ear resolved	2	1	2	1
	Neither resolved	3	3	3	3
Unilateral	Resolved	0	1	1	3
	Not resolved	3	4	1	2
% of children resolved (*n*/*N*)		33.3% (3/9)	22.2% (2/9)	57.1% (4/7)	44.4% (4/9)

TABLE 4 Compliance with autoinflation at 1 month

			Parent-reported frequency at 1 month	
Group	*n*	Reward chart (mean times per day)	Frequency	Mean number of times per day
Improved	6	2.95	All of the time, $n = 5$	3
			Most of the time, $n = 1$	
Not improved	3	2.70	All of the time, $n = 3$	3
			Most of the time, $n = 0$	

Discussion

The pilot study under-recruited compared with the target set of 15 children per group. The main reasons for under-recruitment were twofold. First, delays in obtaining necessary ethics, governance and site permissions resulted in a late recruitment start date of January 2010, leaving only half the anticipated recruitment time frame (OME is a seasonal condition that substantially tails off around April). Second, the lowest recruiting of the four practices involved an enthusiastic GP who, because of time pressures, started recruitment extremely late.

A previous primary care trial estimated the need for 2940 children to be invited, in order to screen 1176 (40%), of whom 294 (25%) would be randomised.[30] Using the pilot CONSORT figures for a revision of the estimates, it was predicted that, of 5570 invitations for screening, 891 (16%) would respond and 294 (33%) would be randomised. This enabled a more precise estimate of practice recruitment and costs for the main study. More 4- to 6-year-olds than anticipated were identified, and approximately half of all those with symptoms who were screened were eligible and subsequently randomised. No parent/guardian of an eligible child refused consent for screening or to participate in the pilot, revealing very high acceptance rates for the study, and overall retention was good.

Web-based randomisation was the preferred option for site staff, and considered a more robust and inclusive system for randomisation, and was therefore implemented in the main study.

Children randomised to autoinflation were noted to be fully compliant with the method of autoinflation. No withdrawals occurred once children had started using the device. Feedback obtained from both parents and children about using the device was incorporated into subsequent training days for the main trial. Feedback included what to expect from the technique; the importance of prior stretching of new balloons; the need to involve the parents in demonstrating the method; and the need for persistence, especially over the first few days.

One child did experience nosebleeds while using autoinflation. The parent reported that the child had suffered from previous recurrent nosebleeds, but chose to continue with the study anyway. Dr Stangerup (Otovent inventor) told us that there had been no previous reports of nosebleeds as a complication of nasal balloon inflation (Professor Sven Eric Stangerup, University of Copenhagen, 2011, personal communication). However, it was decided on review that it would be best to avoid any such prior histories based on a degree of hypothetical risk. A new exclusion criterion was therefore added (*Box 2*).

The trial materials and operating manual were deemed satisfactory and were well accepted. The pilot study highlighted that not all nurses were confident with tympanometry, and three nurses would have liked additional training in use of the machine and interpretation (*Box 3*).

Conclusion

This small-scale study, once under way, was successful in recruiting patients, compliance was excellent and no major protocol changes were needed for the main study and costing was improved. A great number of useful and practical points were learned from the study, in both a systematic and informal way, from parents and nurses. The overall performance of the pilot was encouraging and appeared sufficient in terms of recruitment and in answering what was felt to be the major unknown issue about whether or not children were able perform the technique and achieve sufficient compliance over 1 month in a primary care setting.[35]

BOX 2 Changes to the study requiring NRES approval

1. Change in method of randomisation: a continuously available web-based randomisation, instead of telephone randomisation, would be employed for the main study.
2. Additional exclusion criterion: an additional exclusion criterion would be added to the main study as follows: 'A recent nosebleed in the previous 3 weeks, or more than one episode of nosebleeds in the preceding 6 months'.
3. Web-based hearing test [Two Alternative Auditory Disability and Speech Reception Test (TADAST)]:[27] the TADAST forced-choice hearing disability test (previously evaluated in primary care) would be used as a baseline and 1-month measure. It was agreed that this would be optional in the main study and used in secondary analyses.
4. An improved, pragmatic version of the OM8-30 questionnaire (OMQ-14):[20,21,30] the OMQ-14 became available courtesy of Professor Mark Haggard and was used in the main study. Database analyses showed that the OMQ-14 retained the validity, sensitivity and reliability for the most important symptoms and concerns of relevance for primary care, and was anticipated to have better completion rates that the longer OM8-30 and would be more amenable to primary care use.

BOX 3 Changes to trial logistics for the main study

1. Trial management: the trial management group suggested revising the research management structure to allow for recruitment to be co-ordinated from Southampton with close supervision from the chief investigator once the trial design had been finalised and data collection tools and other trial materials had been finalised. The PCVC-CTU would continue to provide Clinical Trials Unit (CTU) supervision and expertise in data management and statistics.
2. Improved support for nurses: regional training days with an audiologist and the Otovent suppliers, and improved tympanometric support by the management team (fax and telephone) for screening and recruitment purposes were recommended for the main study.
3. Recruitment: more precise recruitment logistics and costing were made for the main study. It was agreed to use trained RNs rather than GPs (for whom time pressures were considered to be greater). Owing to the seasonal nature of OME, it was agreed to push for recruitment before the Christmas period to increase uptake.

Chapter 3 Methods

Study design

We conducted an open, pragmatic RCT in primary care. We examined the difference in effectiveness between regular autoinflation with standard care and standard care alone.

Setting

The study was set in primary care in three regions of England: the South West, Thames Valley and Cheshire regions. The main study recruited children from 43 family practices from 17 UK PCTs, between January 2012 and February 2013.

Ethics approval and research governance

Ethics approval was awarded by the NRES on 10 August 2009, reference number 09/H0504/75 (see *Appendix 1*), and local research governance approval was obtained from all participating PCTs.

Recruitment and training of research nurses

Practices were recruited to the study by the PCRNs. At each practice a GP acting as principal investigator and a RN were assigned to the study. Practices were reimbursed for nurse time by the Department of Health service support costs.

Recruitment of practices

A total of 50 general practices were recruited to the study, of which 43 practices actively screened and randomised children during the study period (*Tables 5* and *6*). During winter 2011, 39 practices received training; seven did not continue to patient screening because of practice withdrawal ($n = 3$), slow start ($n = 2$), staff illness ($n = 1$) or research governance delay ($n = 1$). In order to maximise recruitment, an additional 11 practices were trained in autumn 2012 to replace nine low-/non-recruiting practices from the first season. Reasons for low recruitment included change in nursing staff ($n = 3$), practice withdrawal owing to other commitments ($n = 2$), recruitment problems ($n = 1$) and small practice list size that limited further recruitment ($n = 1$).

Training of research personnel

Five regional training days took place between November 2011 and January 2012 in Southampton ($n = 2$), Chippenham ($n = 1$), Oxford ($n = 1$) and Nantwich ($n = 1$). This provided convenient training locations for RNs and helped establish good and effective communication between RNs and the study team. One practice received on-site training and three practices requested additional pre-study visits from the study manager. One further training day took place in September 2012 (Oxford) for the 11 additional practices.

TABLE 5 Participating practices by PCRN/PCT

PCRN/PCT	Number of practices ($n = 43$)
PCRN South West	27
Bath and North East Somerset	4
Bournemouth and Poole	1
Dorset	1
Gloucestershire	2
Hampshire	9
Somerset	3
Southampton City	1
Wiltshire (North, East and West)	5
Wiltshire (South)	1
PCRN Thames Valley	13
Berkshire East	1
Berkshire West	3
Milton Keynes	1
Oxfordshire	8
Cheshire CLRN	3
Central and Eastern Cheshire	3

CLRN, Comprehensive Local Research Network.

TABLE 6 Characteristics of participating practices

Characteristics	Number of practices ($n = 43$)
Practice list size	
1–4999	3
5000–14,999	32
15,000+	8
Number of GP partners	
0–5	15
6–10	21
11–15	6
16+	1
Deprivation score	
High	1
Mid	11
Low	31
Main duties of participating research staff	
Practice nurse fitting in research around other duties	24
RN within GP practice	13
RN from outside GP practice	3
GP conducting research	3

The training days involved the chief investigator, the trial co-ordinator, an audiologist, PCRN observers and a company representative. Study aims and methods were comprehensively covered. These included procedures for identifying and screening patients, taking consent, how to perform web-based randomisation, patient assessment and data management. A training manual was provided giving full details of the study methods and outcome assessments. Training in otoscopic examination and tympanometry was provided by the chief investigator and an audiologist from Starkey Laboratories Ltd, who gave detailed information and a practical demonstration of the technology and interpretation of the tympanometric results. This included classification of the four main types (A, C1, C2 and B) of tympanograms, recognition of obstructing wax, perforations, grommets and appropriate canal volumes for age, etc. Nurses had the opportunity to practise and refine their techniques during the training day. Brief training in the correct use of the autoinflation device (Otovent) was given by a representative from the suppliers (Kestrel Medical Ltd). All nurses or recruiting GPs had current training in GCP by the start of the trial.

As a means of additional support and training, nurses were invited to fax their initial screening tympanograms to the co-ordinating centre, where they were independently reviewed for categorisation based on all available parameters and observations. Any discrepancies in tympanometric classification were then fed back to nurses to help improve their precision of diagnosis in the field. Extra on-site training was offered by two experienced members of the study team where requested. Regional meetings were scheduled at the start of the second recruitment season to provide a study update and a further review of tympanometry and interpretation.

Recruitment of children

Participating practices were asked to invite 140 children as a target for screening. It was conservatively estimated from the pilot study that the proportion of invited children who would be recently symptomatic and/or whose parents would have concerns and who would, therefore, attend for screening would be 16%, and that one-third of these would be eligible for randomisation (140 children invited; 22 screened; and seven randomised in each participating practice, i.e. 1 in 20 children).

Children were identified by practice-based computer search or opportunistic case finding by practitioners, nurses and health visitors as follows.

Computer searches

- High-risk children, that is those aged 4–6 years, were identified from practice age/sex registers and those with one or more OME-related symptoms or concerns in the previous 3 months were invited for screening.
- An audit of the attendance records of 7- to 11-year-old children identified those with ear-related problems in the previous year.

Opportunistic case finding

- General practitioners, nurses and health visitors identified children leading to an in-practice referral to the RN.

The parents of children identified for the study received an invitation letter and information sheet, and children received an age-appropriate information sheet (see *Appendices 2* and *3*). Parents gave written informed consent for screening and children were invited to give written assent if deemed appropriate by the RN (see *Appendix 4*). *Table 7* shows features of study entry by practice and PCT.

TABLE 7 Number of practices, children screened and randomised per PCT

PCRN/PCTs	Participating practices	Number of children screened	Number of children randomised
PCRN South West	27	843	212
Bath and North East Somerset	4	84	18
Bournemouth and Poole	1	5	0
Dorset	1	66	11
Gloucestershire	2	92	22
Hampshire	9	316	81
Somerset	3	126	34
Southampton City	1	24	5
Wiltshire (North, East and West)	5	116	37
Wiltshire South	1	14	4
PCRN Thames Valley	13	253	77
Berkshire East	1	11	1
Berkshire West	3	23	6
Milton Keynes	1	8	3
Oxfordshire	8	211	67
Cheshire CLRN	3	139	31
Central and East Cheshire	3	139	31
Total	43	1235	320

CLRN, Comprehensive Local Research Network.

At the screening visit, the RN checked both ears for any obstructing wax, perforations or grommets using otoscopy. If the ear canal was occluded with wax, olive oil ear drops were recommended to soften and disperse the wax, and rescreening was rescheduled. Tympanometric screening was performed to assess full eligibility for the study, that is, every symptomatic child had to have one or two type B tympanograms confirming the presence of uni- or bilateral OME (*Table 8* shows details of tympanometric classification used). This examination was requested to be repeated wherever the interpretation was unsatisfactory or inconclusive. The inclusion and exclusion criteria are shown in *Box 1*.

TABLE 8 Tympanometric classification[a] (based on modified Jerger classification[63–65])

Tympanometric classification	Middle ear pressure	Tympanogram	Positive predictive value for OME
Type A	+200 to –99	Peak	Normal
Type C1	–100 to –199	Peak	Normal
Type C2	–200 to –399	Peak	54%
Type B	–400	Flat trace	88%

a As used in primary care trials[18,36] and the autoinflation Cochrane systematic review.[35]

Randomisation and masking

Eligible children were individually randomised to autoinflation plus routine care or routine care alone within 1 week of screening. An independent external agency provided a centralised web-based randomisation system (www.sealedenvelope.com) for nurses to access while recruiting children to the study. The Oxford Primary Care CTU independently managed, co-ordinated, analysed and checked the data validity. The randomisation used an algorithm with minimisation based on three potential effect modifiers/confounders: age (< 6.5 years vs. > 6.5 years), sex and baseline severity of OME (one vs. two baseline type B tympanograms).[18] Owing to the nature of the intervention, use of placebo was not possible and therefore nurses, children and families were not masked to treatment allocation.

Trial intervention

The simple autoinflation treatment used in this trial involved inflating a purpose-manufactured balloon (Otovent), by blowing through each nostril into a connecting nozzle three times per day for 1–3 months (*Figure 3*).[55,56,60,61,73] Children in the treatment arm were instructed by watching the nurse and/or parent demonstrate the procedure, starting with stretching the balloon (by hand or mouth blowing). A website, which included a short instruction video, was also available as a back-up for parents and children (www.gluear.co.uk). A sticker book was provided to encourage the child's ongoing participation. Children still recording a type B tympanogram in either ear at 1 month were advised to continue with nasal balloon autoinflation for a further 2 months. All study children (both arms) received their usual/routine clinical care as normal. At the end of the 3-month clinical study period, children in the standard care arm with tympanometric evidence of glue ear were offered a 1-month supply of nasal balloons.

Assessments

Baseline assessment was conducted within 1 week of screening. Parents of children in the intervention group were routinely contacted by telephone after 3 days to provide additional support for autoinflation, if required. All children were followed up at 1 and 3 months (*Figure 4*).

FIGURE 3 Nasal balloon autoinflation (Otovent). Reproduced with permission from Kestrel Medical Ltd.

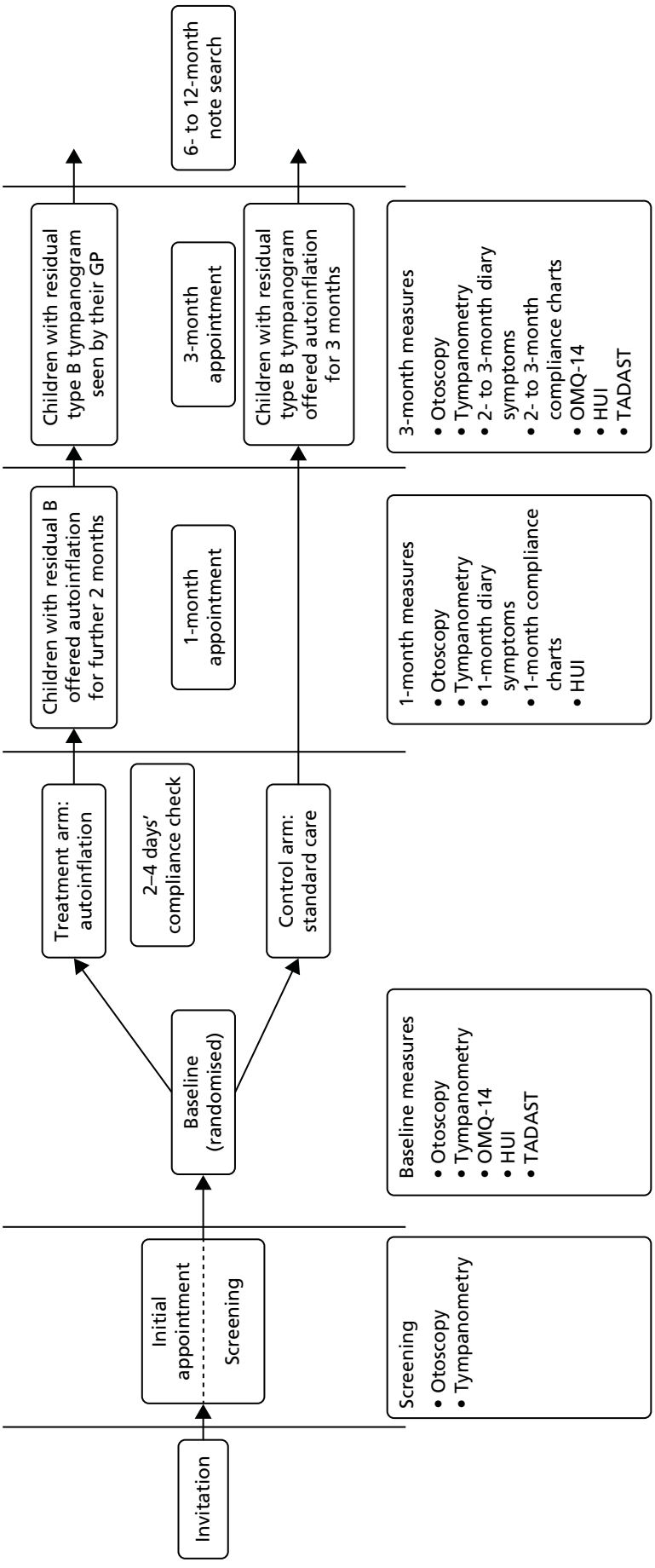

FIGURE 4 Flow of participants through the main study.

Advanced appointments were made for the next follow-up assessment at each visit and an appointment card given. A postcard reminder was sent 1 week before the next appointment to encourage attendance. In the case of non-attendance, the RN was asked to attempt contact twice by telephone and twice with a missed appointment card, after which the patient was considered lost to follow-up.

Withdrawals

In accordance with GCP, parents/guardians were free to withdraw their children from the study at any time without affecting their medical care. Children were withdrawn from the study in the event of incorrect diagnosis at the time of randomisation (no type B tympanogram confirmation).

Outcome measures

Children were assessed for the most important clinical outcomes at 1 and 3 months post randomisation over a recommended 3-month waiting or monitoring period, over which time natural resolution effects would be expected to occur in some children.[3,5,6] It was anticipated that, if the method was effective, it would most likely be at 1 month, when taking into account poor compliance reported in one secondary care study,[58] and implied or suggested concerns for general use and durability of the method in primary care.[1,35,37,74] Health economic outcomes were collected for 1, 3 and 12 months. With the protocol indicating that routine care should not be affected in any way during the clinical phase (3 months) of the study, referrals in particular would be difficult to assess without longer-term follow-up (12 months). The flow diagram for the main study was essentially unchanged from the pilot except that (1) the OMQ-14 replaced the OM8-30 at baseline and 3 months; (2) the TADAST hearing performance test (see *Two alternative auditory disability and speech reception tests hearing test*) was added at baseline and 1 month; and (3) a notes audit for HE purposes was completed up to 12 months post randomisation.

Main outcomes

Primary outcomes in children at 1 and 3 months

(a) The primary outcome was dichotomous: the difference in the proportion of children showing definite tympanometric resolution (from a type B tympanogram to a type A or C1 tympanogram, i.e. back to normal middle ear pressures) in at least one affected ear at 1 month. Intermediate negative-pressure C2 tympanograms were considered insufficient evidence of resolution of fluid, that is, not classified for analysis purposes as resolved (see *Table 7*).[69,71] Tympanometry has better test characteristics for the presence of effusion than history and/or simple otoscopy, and is thus a good choice for primary care studies, in which it has been shown to be a reliable diagnostic instrument.[1,18,24,31,36] It provides a reasonably objective outcome measure that can also be assessed blind to allocation arm. Two members of the trial team, trained in tympanometry, independently reviewed anonymised tympanometry printouts (for the main 1- and 3-month outcomes, see *Tympanometric assessments*). Cases of disagreement were settled by an independent audiologist. All MTP-10 micro-tympanometers (Interacoustics, Assens, Denmark), previously used in the GNOME study,[18,30] were recalibrated by PC Werth Ltd prior to the start of the study and subsequently on an annual basis while in use.

(b) The difference in the proportion of children showing definite tympanometric resolution (of a type B tympanogram to a type A or C1, i.e. back to normal middle ear pressures) in at least one affected ear at 3 months was considered a second main outcome and is justified as above and in accordance with guideline suggestions for the monitoring period duration.[1,2]

Secondary outcomes

Tympanometric resolution based on ears as the unit of analysis

Differences in the proportions of ears by group that show resolution (from type B to A/C1) at 1 and 3 months was a secondary outcome. This is justified as a means of demonstrating efficacy that provides additional power by using the data from both ears. Ears are not independent variables and previous trials that have not taken into account the correlation between ears in the analysis, resulting in overly precise CIs, have been justifiably criticised. Such outcomes are included in the main Cochrane meta-analyses, with post-hoc adjustments to account for this correlation.[35] Generalised estimating equations can be used to adjust the analysis for the non-independence of ears in a pre-specified manner. Thus, these robust outcomes are useful to demonstrate efficacy of the method in actually clearing children's ears of effusions. However, such, and indeed all, tympanometric outcomes require additional clinical confirmation of effectiveness to better inform a child-centred management model of OME.[19,34,35,75]

Non-tympanometric clinical outcomes

Ear-related QoL was measured at 3 months using the OMQ-14 (see *OMQ-14 impact measures*). Parents completed weekly diaries to record symptoms, adverse events and compliance, and also HUI version 3 (HUI3),[76,77] with resource use questionnaires at baseline, 1 and 3 months to inform a HE analysis. Pure-tone audiometry was not conducted, as it cannot be done with adequate precision in non-specialist and noisy settings, and correlates only weakly with child and family QoL.

OMQ-14 impact measure

The OMQ-14 is a 14-item PROM developed by a process of extensive statistical refinement and iteration from two large primary and secondary care UK trials on OME [GNOME/TARGET (Trial of Alternative Regimens of Glue Ear Treatment)][9,18] and further evaluated in ongoing cohort/audit data sets from across Europe (Eurotitis 2) (Professor Mark Haggard, University of Cambridge, 2010, personal communication).[21] It is a functional health status measure that is reported by proxy. As a shortened form of the OM8-30,[18,19,21,30,75,78] the 14 items selected have been demonstrated to efficiently optimise item mapping on to the HUI.[20] As a questionnaire it is simpler to administer and has better completion rates with fewer missing data than the longer OM8-30 (cf. HTA report for GNOME, where the missing outcome data was disappointing).[30] Its brevity also makes it more suitable for primary care use. It measures three domains found to map on to QoL in primary care: reported hearing difficulty and speech concerns; behavioural and developmental impact; and ear-related physical ill health.[21] It was decided a priori in the statistical plan to use the total instrument score (the OMQ-14 score used here is not the total integer 'quick score' intended for rapid field use, but the more precise decimal QoL-weighted sum of the three factor scores mentioned; the used version is slightly more precise) as the single most useful measure for family practice (and to avoid data dredging). The OMQ-14 total score refers to the 3-month period prior to completion, and in this study was completed at baseline and at 3 months (see *Appendix 5*). A standard deviation (SD) change of ≈0.3 in score is considered a clinically important effect for the child and family in terms of ear-related QoL.

Parent-reported symptom diary

Parents were asked to complete a weekly diary recording the number of days (0–7) of their child's main symptoms of hearing loss, earache, difficulty concentrating, pain relief, disturbed sleep and absence from school.

In addition, a second diary of items was included to systematically record a number of other symptoms including nosebleeds, clumsiness/off-balance, systemic illness, nasal discharge and nasal congestion/snoring. Symptoms considered potentially adverse were collected on an adverse event form and some of these overlapped with the diary symptoms.

Two alternative auditory disability and speech reception tests hearing test

Hearing disability was evaluated at baseline and at 1 month for all children using the TADAST web-based test. TADAST is a forced-choice test, originally developed in primary care, that evaluates hearing disability associated with glue ear, and which has shown good test–retest repeatability in 4- to 11-year-old children.[27,79] Parents received an instruction card with details to log on to the new website at home after the baseline and 1-month assessments.

Compliance with the intervention

Compliance measures allow for the assessment of experiences of using the Otovent device (see *Chapter 6*), as concerns have been raised regarding what age autoinflation can be reliably performed.[80] All parents in the intervention group were contacted 2–4 days after the baseline visit primarily as a supportive measure but also to assess their compliance. If the parent reported problems with the autoinflation technique or adherence, a follow-up visit with the RN was offered so the parent/child could be given further specific tips and education about improving the technique, based directly on observation of use.

A sticker book diary was used to record compliance with the intervention, with children placing a sticker in the diary each time they inflate the nasal balloon. Parent-reported adherence was also recorded at the 1- and 3-month assessments (when use of the device was recorded as not at all, some of the time, most of the time and all of the time) and compared with the sticker book diary.

Parents of children in the standard care group were asked if Otovent had been used independently either because of self-purchase or because it was inadvertently prescribed during the study period.

Adverse events

The RN specifically asked parents about the occurrence of upper respiratory tract infections (URTIs) and nosebleeds at the 1- and 3-month assessments. In addition, the RN inspected the symptom diary for any further information. Serious adverse events were reported by fax to the co-ordinating centre within 24 hours of the practice being made aware of the event. The co-ordinating centre's standard operating procedures were followed with respect to reporting to the sponsor, the Research Ethics Committee, the Data Monitoring and Ethics Committee (DMEC)/Trial Steering Committee and governance offices. Annual safety reports were submitted to the Research Ethics Committee.

Changes to the protocol

The majority of these were made as a result of the pilot study and are described in *Chapter 2*. During the main study a total of four substantial amendments were approved by the ethics committee and comprised minor changes to the study documentation, addition of a qualitative evaluation, a 12-month notes review (instead of 6 months post baseline) and a refinement to the study closure strategy, which allowed for a slight overshoot of recruitment. Full details are presented in *Appendix 1*.

Data management, cleaning and validation

All trial data were captured on paper case-report forms or participant-completed questionnaires. Trial data were tracked and managed using a clinical data management system [Open Clinica Enterprise™ (OpenClinica LLC version 3.1, Waltham, MA, USA)]. Preliminary monitoring of received trial data was performed to assess completeness of forms, and compatibility and consistency of paperwork bundles in relation to participant identifiers. All trial data were double entered by two independent users. Self-evident modifications to captured data (correction of spelling errors, conversions, date formats, obvious updates based on supplementary data) were applied to reduce the number of data queries sent to the research sites.

Responsible personnel at each research site reviewed and authorised a list of all prospective modifications. Validation of data was performed in three main ways:

- On entry, programmed rules and range checks to highlight missing or inconsistent data would fire if predetermined conditions were met.
- Listing checks were employed to identify potential discrepancies across participant visits/forms.
- Review of the data set to identify discrepant, missing or outlying data was performed when participants completed their study schedule.

Requests for missing responses or clarification of inconsistent data (queries) were sent to the RNs at regular intervals to increase the likelihood of resolution.

Tympanometric assessments

Screening: finding cases

Tympanograms from 1104 of 1235 children screened (89%) were faxed to the co-ordinating centre soon after initial assessment as part of ongoing training in interpretation and to improve precision of diagnosis prior to randomisation. Only 55 of 2207 (2.5%) tympanograms (ears) were uninterpretable owing to poor technique or wax on expert review. All available data were used in the assessments, including otoscopic findings, shape of the curve, pressures, gradients and canal volume. The tympanogram classifications recorded in the database reflect the assessment made by the trial manager and/or chief investigator. Where these differed from the nurse classification, a data query was issued.

Outcome assessments

Tympanogram data captured from all follow-up assessments were retained as captured by the RN at the time of the patient assessment and a data query was issued only in the case of missing classifications. Tympanogram data collected during the follow-up assessments were reviewed in a separate fully anonymised process by the trial manager and chief investigator. For all tympanogram type classifications (A, C1, C2 and B), the expert inter-rater agreement was 89%. In all cases of disagreement, a blinded independent audiologist adjudicated. The reviewed outcome data were blinded to study identification number and treatment group. The final determined classifications for reviewed tympanogram data were entered into the clinical database using double data entry, consistent with all other data. These blinded agreed expert data assessments were the ones used in the final efficacy analyses at 1 and 3 months.

With regard to nurse interpretation of tympanometry and classification of all available ears, the summary level of agreement beyond chance between the nurse interpretation and the agreed blinded expert interpretation as the standard found substantial agreement that improved throughout the study (*Table 9*).[81]

Once all the follow-up assessment data were received, a 100% critical item review was performed on all tympanogram data and any inconsistencies rectified, particularly in the case where multiple tympanogram readings were taken during one assessment. The entire data set was then reviewed for inconsistencies and any further missing data points, before conducting a final quality control check on all data received for 19 patients randomly selected from all those recruited to the study. The final error rate was calculated to be 0.00% for critical items (tympanogram data) and 0.04% across all data points.

TABLE 9 Nurse- vs. expert-blinded interpretation of all tympanograms post randomisation

Time point	*n* (ears)	Kappa (95% CI)
1 month	548	0.706 (0.689 to 0.771)
3 months	497	0.792 (0.782 to 0.823)

Statistical validation

Validation of all results presented in this report was conducted by Ly-Mee Yu, Oxford CTU. All results/major end points/primary end points were validated by independent programming using Stata version 13.0 (StataCorp LP, College Station, TX, USA).

Statistical methods

A detailed statistical analysis plan was developed at the start of the study.

Definition of populations used

Screened population

The screened population comprises all children who attended for the initial appointment and gave written informed consent.

Intention-to-treat population

The intention-to-treat (ITT) population comprises all children, out of those randomised, for whom tympanometric readings are available.

Per-protocol population

The per-protocol (PP) population comprises those randomised who satisfied the study eligibility criteria, received their allocated intervention, who did not used any autoinflation devices other than those provided for the study purposes and who used autoinflation at least twice per day for at least 70% of their treatment period during the first month. Children who presented more than 7 days before or after the scheduled 1-month visit date were considered not to have complied with the trial protocol and were excluded from the PP population.

Safety population

The safety population comprises all randomised children.

Primary analyses

The primary analysis was based on the ITT population. The proportion of children in each group with tympanometric resolution in at least one affected ear at 1 month (primary outcome) was compared using a generalised linear model with log-link function.[82] Results are presented as adjusted RRs with 95% CIs. The regression model[83] adjusts for pre-specified baseline covariates: tympanometric baseline severity (one or two type B tympanograms), age, sex and PCT. Sensitivity analyses are performed on ITT and PP populations.

Multiple imputation of all missing data was performed using baseline variables as per the statistical plan: use of antibiotics, eczema, hay fever, asthma, age, sex, baseline severity, baseline OMQ-14 and follow-up OMQ-14 weighted scores. Multiple imputed data sets were created using Stata version 13 and the 'ice' and 'mim' functions.[84]

For the 1-month ear-based analysis of tympanometric resolution, the non-independence (correlation) of the ears was adjusted for using generalised estimating equations with an independent working correlation structure.[85,86]

Secondary analyses

Subgroup analyses

Four subgroups were compared using interaction tests on the primary outcome of resolution in at least one 'B' ear by 1 month. The subgroups considered were those described in the protocol, namely:

1. age: < 6.5 years or ≥ 6.5 years
2. severity: one or two B-type ears at baseline
3. OMQ-14 standardised total score: < 0 or ≥ 0
4. sex.

No interaction tests were significant; thus, results are not presented according to subgroups. The *p*-values ranged from 0.25 to 0.50.

Tympanometric resolution at 3 months

The analysis of the 3-month secondary end points by both child and ear were analysed in the same way as the primary end point using a generalised linear model that adjusts for a limited number of pre-specified baseline covariates.

Other tympanometric outcomes were analysed as per the statistical plan. Tympanometric deteriorations in normal ears at baseline were evaluated for potential confounding of results. However, as very few deteriorations occurred, no further analyses of this end point were undertaken.

Quality of life (OMQ-14)

The OMQ-14 standardised total scores at baseline and 3 months were calculated based on weightings provided by Professor Mark Haggard and Helen Spencer of the Eurotitis-2 Study Group (Cambridge University, 2011, personal communication). Standardised OMQ-14 change from baseline scores were analysed using a linear mixed-effects model with PCT as a random effect, and age, sex, baseline severity and OMQ-14 baseline score as fixed effects. Summary statistics for baseline and follow-up (3-month) standardised OMQ-14 scores are presented. Higher scores represent worse outcomes. The average change from baseline score is compared between groups. Questionnaires with more than four missing items were pre-specified as indicating separate analysis; however, this applied to only one person so no sensitivity analysis was carried out.

Diary card

Diary card symptom counts were quite skewed, with fewer children/parents reporting multiple diary symptoms. For this reason standard linear models could not be used to analyse these data and they were instead classified into categories based on the total number of weeks with symptoms (0, 1–7, 8–28, 29 + days). Category boundaries were decided on prior to data lock and were detailed in the amendment to the statistical analysis plan.

Data were analysed using an ordinal logistic regression model.[87] The model is an extension of the standard logistic regression model used for binary data, but allows for more than two categories for the outcome. The OR from an ordered logistic regression expresses the odds of being in a higher ordered category (i.e. more days with symptoms) when in the autoinflation group compared with the standard care group. Models were adjusted for age and sex as before.

Outputs from the analyses are displayed alongside a summary of the data for the 1- and 3-month diary cards.

Two Alternative Auditory Disability and Speech Reception Test

The TADAST score was a continuous variable out of a total of 36, with a chance score of 16 out of 36 to be compared between groups. However, because of problems with the website and late ethics permission, insufficient numbers of children completed the follow-up test (seven children at 1 month and two children at 3 months), so results are not presentable.

Adverse events and safety

There are no a priori hypotheses to test. Potential but speculative adverse outcomes from the literature are therefore described in simple frequency tables.[55,56]

Sample size calculation

A 45% control resolution (improvement) rate at 1 month was anticipated in the calculations, as found in the previous GNOME trial.[18] The best estimates for the expected difference at 1 month were based on a meta-analysis of four small secondary care trials that used Otovent, included in the update for Cochrane.[35] Thus, for resolution at 1 month, the most conservative evidence-based estimate of effect size was an OR of 2.4. Given this effect size, 250 children were required (125 in each group) for a standard $\alpha = 5\%$ and power = 90%. With 15% lost to follow-up, 295 were needed in total (for power = 80%, 226 were needed in total). The sample was also powered to detect a ≈0.3 SD effect on continuous variables such as the OMQ-14 total score at 3 months, which was deemed clinically significant.

Changes to the statistical analysis plan

1. Analyses were not completed using Stata version 11.2 (which is now an old version) but rather SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and Stata version 13 (StataCorp LP, College Station, TX, USA).
2. Twenty multiply imputed data sets were created for the sensitivity analysis of the primary end point rather than the five data sets specified, as more data sets result in more robust estimates.

Chapter 4 Results

Recruitment and trial flow profile

Screening commenced in December 2011. The first patient was randomised in January 2012 and the last child was randomised in February 2013. A total of 1235 children were screened, with 320 children (26%) randomised into the study over a period of 13 months. *Table 10* displays the characteristics of screened children. The main reasons for ineligibility were no type B tympanogram, not currently at school or a recent nosebleed. Ineligible children reported fewer symptoms associated with OME in the preceding 3 months, and had fewer consultations for otitis media and OME in the previous 12 months.

The study population comprised 167 (52%) boys and 153 (48%) girls, with an age range of 4–10 years (mean 5.40 years; median 5.71 years); 181 (57%) children had unilateral OME and 135 (42%) had bilateral OME [on review, four children (1%) recruited were deemed not to have OME on tympanometry]. Two hundred and fourteen (67%) were recruited between October and March, while 106 (33%) were recruited between April and September.

The baseline characteristics of randomised children were well balanced between the two groups (*Tables 11* and *12*) with six being the median number of symptoms and concerns [interquartile range (IQR 4–8)] in the routine care arm and seven (IQR 5–9) in the intervention arm. The trial demographic data were comparable to national figures, but 33% of participating parents (vs. 27% nationally) were educated to degree level or higher.[88]

TABLE 10 Baseline characteristics: screened children

Variable	Randomised, *n* (%) (*N* = 320)	Screened only, *n* (%) (*N* = 1235)
Sex		
Female	153 (47.8)	429 (46.9)
Male	167 (52.2)	485 (53.0)
Missing	0 (0.0)	1 (0.1)
Age (years)		
4	58 (18.1)	158 (17.3)
5	147 (45.9)	370 (40.4)
6	77 (24.1)	250 (27.3)
7	21 (6.6)	53 (5.8)
8	8 (2.5)	23 (2.5)
9	6 (1.9)	29 (3.2)
10	3 (0.9)	13 (1.4)
11	0 (0.0)	16 (1.7)
12	0 (0.0)	2 (0.2)
Missing	0 (0.0)	1 (0.1)

continued

TABLE 10 Baseline characteristics: screened children (*continued*)

Variable	Randomised, *n* (%) (*N* = 320)	Screened only, *n* (%) (*N* = 1235)
Was this child recruited from:		
4- to 6-year-old list	265 (82.8)	758 (82.8)
7- to 11-year-old list	21 (6.6)	103 (11.3)
GP/nurse/health visitor referral	34 (10.6)	50 (5.5)
Missing	0 (0.0)	4 (0.4)
A prolonged or bad cold, cough or chest infection		
No	37 (11.6)	178 (19.5)
Yes	262 (81.9)	662 (72.3)
Missing	21 (6.6)	75 (8.2)
Appears to be lip reading		
No	240 (75.0)	756 (82.6)
Yes	57 (17.8)	84 (9.2)
Missing	21 (6.6)	75 (8.2)
An earache		
No	124 (38.8)	504 (55.1)
Yes	175 (54.7)	336 (36.7)
Missing	23 (7.2)	75 (8.2)
Not doing as well at school as you or the teacher reasonably think		
No	219 (68.4)	680 (74.3)
Yes	79 (24.7)	157 (17.2)
Missing	22 (6.9)	78 (8.5)
Often mishears what is said		
No	61 (19.1)	323 (35.3)
Yes	238 (74.4)	516 (56.4)
Missing	21 (6.6)	76 (8.3)
Has noises in the ear or is dizzy		
No	225 (70.3)	674 (73.7)
Yes	73 (22.8)	163 (17.8)
Missing	22 (6.9)	78 (8.5)
Hearing loss is suspected by anyone		
No	154 (48.1)	606 (66.2)
Yes	144 (45.0)	232 (25.4)
Missing	22 (6.9)	77 (8.4)
Snores, blocked nose or poor sleep		
No	81 (25.3)	318 (34.8)
Yes	218 (68.1)	522 (57.0)
Missing	21 (6.6)	75 (8.2)
Says ‘eh what?’ or ‘pardon’ a lot		
No	50 (15.6)	252 (27.5)
Yes	249 (77.8)	587 (64.2)
Missing	21 (6.6)	76 (8.3)

TABLE 10 Baseline characteristics: screened children (*continued*)

Variable	Randomised, *n* (%) (*N* = 320)	Screened only, *n* (%) (*N* = 1235)
Speech seems behind other children's		
No	239 (74.7)	689 (75.3)
Yes	60 (18.8)	152 (16.6)
Missing	21 (6.6)	74 (8.1)
Needs the television turned up		
No	119 (37.2)	505 (55.2)
Yes	180 (56.3)	333 (36.4)
Missing	21 (6.6)	77 (8.4)
Any suspected ear problem		
No	177 (55.3)	675 (73.8)
Yes	122 (38.1)	164 (17.9)
Missing	21 (6.6)	76 (8.3)
May be irritable or withdrawn		
No	207 (64.7)	633 (69.2)
Yes	92 (28.8)	205 (22.4)
Missing	21 (6.6)	77 (8.4)
Observational register – was the child recruited from:		
Computer records	284 (88.8)	859 (93.9)
Referral	36 (11.3)	53 (5.8)
Missing	0 (0.0)	3 (0.3)
How many episodes of OME have they had in the last 12 months?		
0	234 (73.1)	787 (86.0)
1	42 (13.1)	69 (7.5)
2	17 (5.3)	14 (1.5)
3	3 (0.9)	10 (1.1)
4	6 (1.9)	2 (0.2)
6	1 (0.3)	0 (0.0)
7	0 (0.0)	1 (0.1)
Missing	17 (5.3)	32 (3.5)
How many episodes of OM have they had in the last 12 months?		
0	195 (60.9)	678 (74.1)
1	67 (20.9)	154 (16.8)
2	27 (8.4)	34 (3.7)
3	7 (2.2)	15 (1.6)
4	6 (1.9)	3 (0.3)
5	0 (0.0)	1 (0.1)
6	0 (0.0)	1 (0.1)
7	1 (0.3)	0 (0.0)
Missing	17 (5.3)	29 (3.2)

continued

TABLE 10 Baseline characteristics: screened children (*continued*)

Variable	Randomised, *n* (%) (*N* = 320)	Screened only, *n* (%) (*N* = 1235)
Entries in their notes over the last 12 months for hearing loss		
No	243 (75.9)	794 (86.8)
Yes	61 (19.1)	85 (9.3)
Missing	16 (5.0)	36 (3.9)
Entries in their notes over the last 12 months for snoring		
No	292 (91.3)	848 (92.7)
Yes	12 (3.8)	30 (3.3)
Missing	16 (5.0)	37 (4.0)
Entries in their notes over the last 12 months for behaviour concerns		
No	298 (93.1)	846 (92.5)
Yes	6 (1.9)	31 (3.4)
Missing	16 (5.0)	38 (4.2)
Entries in their notes over the last 12 months for speech concerns		
No	289 (90.3)	834 (91.1)
Yes	15 (4.7)	43 (4.7)
Missing	16 (5.0)	38 (4.2)
Entries in their notes over the last 12 months for educational concerns		
No	295 (92.2)	850 (92.9)
Yes	9 (2.8)	27 (3.0)
Missing	16 (5.0)	38 (4.2)

TABLE 11 Baseline characteristics: randomised children by treatment group

Variable	Standard care (*n* = 160)	Autoinflation (*n* = 160)
Age		
Years, mean (SD)	5.4 (1.04)	5.4 (1.24)
Sex		
Male	83 (51.9)	84 (52.5)
Severity of OME (number of type B tympanograms)		
No type B ears	2 (1.3)	2 (1.3)
One type B ear	91 (56.9)	90 (56.3)
Two type B ears	67 (41.9)	68 (42.5)
Month randomised		
October to March	107 (66.9)	107 (66.9)
April to September	53 (33.1)	53 (33.1)

TABLE 11 Baseline characteristics: randomised children by treatment group (*continued*)

Variable	Standard care (*n* = 160)		Autoinflation (*n* = 160)	
Ethnicity				
White	144 (90.0)		152 (95.0)	
Bangladeshi/Indian	2 (1.3)		2 (1.3)	
Mixed race	3 (1.9)		1 (0.6)	
Other group	2 (1.3)		2 (1.3)	
No information	9 (5.6)		3 (1.9)	
Education level of parent/carer				
School to 16 years, no qualifications	11 (6.9)		6 (3.8)	
School to 16 years, GCSEs/O-level	28 (17.5)		33 (20.6)	
Sixth form school or college, A-level	19 (11.9)		25 (15.6)	
Highers, SCOTVEC or NVQ	37 (23.1)		38 (23.8)	
University degree	37 (23.1)		31 (19.4)	
Professional or postgraduate degree	17 (10.6)		22 (13.8)	
No information	30 (18.8)		31 (19.4)	
Parent-reported child characteristics		***Missing***		***Missing***
Asthma	19 (11.9)	9 (6)	16 (10.0)	4 (3)
Eczema	15 (9.5)	9 (6)	20 (12.5)	4 (3)
Hay fever	40 (25)	9 (6)	42 (26.3)	3 (2)
Antibiotics in previous month	12 (7.5)	9 (6)	21 (13.1)	3 (2)
Parent-reported symptoms in the previous 3 months (4- to 6-year-olds only)	***(n = 135)***	***Missing, n (%)***	***(n = 130)***	***Missing, n (%)***
A prolonged or bad cold, cough or chest infection	113 (83.7)		119 (91.5)	
Appears to be lip reading	27 (20.0)		27 (20.8)	1 (0.8)
An earache	74 (54.8)		77 (59.2)	
Not doing as well at school as expected	32 (23.7)	1 (0.7)	39 (30.0)	
Often mishears what is said	98 (72.6)		112 (86.2)	
Has noises in the ear or is dizzy	29 (21.5)		30 (23.1)	
Hearing loss is suspected by anyone	56 (41.5)	1 (0.7)	67 (51.5)	
Snores, blocked nose or poor sleep	93 (68.9)		101 (77.7)	
Says 'eh what?' or 'pardon' a lot	107 (79.3)		114 (87.7)	
Speech seems behind other children's	22 (16.3)		31 (23.8)	
Needs the television turned up	78 (57.8)		82 (63.1)	
Any suspected ear problem	48 (35.6)		55 (42.3)	
May be irritable or withdrawn	43 (31.9)		38 (29.2)	
Median number of symptoms, *n* (IQR)	6 (4–8)		7 (5–9)	
OMQ-14				
Standardised score, SD (*n*)	–0.04, 0.95 (153)		0.07, 1.00 (153)	

A-level, advanced level; GCSE, General Certificate of Secondary Education; NVQ, National Vocational Qualification; O-level, ordinary level; SCOTVEC, Scottish Vocational Education Council.
Columns are *n* (%) unless otherwise indicated.

TABLE 12 Frequency of consultations in the 12 months prior to baseline assessment

Reason for visit	Standard care ($n = 160$)	Autoinflation ($n = 160$)
Episodes of OME, *n* (%)		
0	120 (75.0)	114 (71.3)
1	21 (13.1)	21 (13.1)
≥ 2	13 (8.1)	14 (8.8)
No information	6 (3.8)	11 (6.9)
Episodes of otitis media, *n* (%)		
0	101 (63.1)	94 (58.8)
1	30 (18.8)	37 (23.1)
≥ 2	22 (13.8)	19 (11.9)
No information	7 (4.4)	10 (6.3)
Hearing loss, *n* (%)		
0	124 (77.5)	119 (74.4)
≥ 1	30 (18.8)	31 (19.4)
No information	6 (3.8)	10 (6.3)
Snoring, *n* (%)		
0	146 (91.3)	146 (91.3)
≥ 1	8 (5.0)	4 (2.5)
No information	6 (3.8)	10 (6.3)
Behaviour concerns, (%)		
0	149 (93.1)	149 (93.1)
≥ 1	5 (3.1)	1 (0.6)
No information	6 (3.8)	10 (6.3)
Speech concerns, (%)		
0	148 (92.5)	141 (88.1)
≥ 1	6 (3.8)	9 (5.6)
No information	6 (3.8)	10 (6.3)
Educational concerns, (%)		
0	149 (93.1)	146 (91.3)
≥ 1	5 (3.1)	4 (2.5)
No information	6 (3.8)	10 (6.3)

Exclusions, withdrawals, loss to follow-up and missing outcomes

Details of all these with reasons are included in the CONSORT trial profile provided (*Figure 5*). Retention in the study was good, with 27 of 320 (8.4%) lost to follow-up at 1 month and 39 of 320 (12.2%) by 3 months. Uninterpretable tympanograms owing to poor technique (leakage or low canal volume) and clinical problems (wax or perforation) were similar in both groups, leaving 131 children in the autoinflation arm and 132 in the routine care arm in the ITT analysis for the primary outcome.

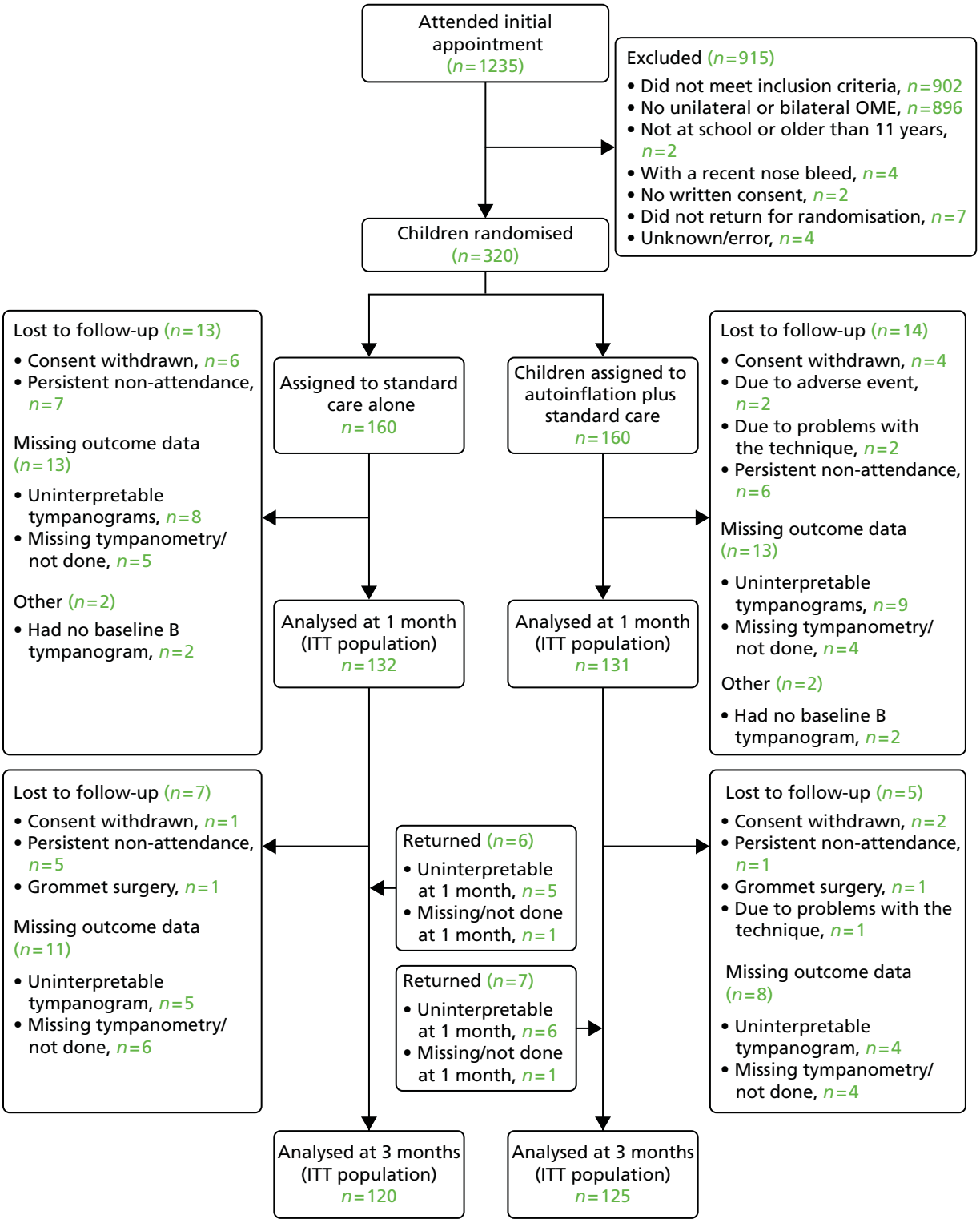

FIGURE 5 Main study CONSORT diagram.

Time of follow-up assessments

Follow-up assessments were scheduled at 1 month (28 days) and 3 months (84 days) after randomisation. *Table 13* shows the range the follow-up assessments timing. Parents were encouraged to return for assessment as close as possible to the scheduled date. Nine patients missed their 1-month assessment but returned for the 3-month assessment. In these cases, the 1-month data were considered as missing. Thirteen children with missing or uninterpretable tympanograms at 1 month returned at 3 months and were included in the analysis.

Main trial results

Primary outcome

Proportions of children showing clearance/resolution of at least one type B tympanogram (effusion) back to normal A/C1 pressures at 1 month

In the ITT population, 109 of 263 children experienced resolution of their B-type ears to A or C1 at 1 month: 62 of 132 (47%) children in the autoinflation group and 47 of 131 (36%) children in the standard care group. At 1 month, those in the autoinflation group were 36% more likely to have resolution of at least one B-type ear (RR 1.36, 95% CI 0.99 to 1.88; $p = 0.0582$). Sensitivity analyses using multiple imputations and a PP population analysis showed no significant difference between groups (*Table 14*).

TABLE 13 Timing of assessments (days post randomisation)

Treatment group	Variable	*n*	Mean	SD	Minimum	Maximum
Standard care	1-month visit	141	32.4	8.3	19	77
	3-month visit	126	95.0	16.4	66	196
Autoinflation	1-month visit	140	32.4	7.6	21	82
	3-month visit	131	98.3	17.3	80	222

TABLE 14 Analysis of primary outcome at 1 month

Analysis	*n*	Adjusted RR	95% CI	*p*-value
ITT population				
Primary analysis (adjusted[a])	263	1.36	0.99 to 1.88	0.0582
[Proc glimmix, dist = bin link = log]				
Sensitivity analysis (multiple imputation[a,b])	$N = 320$ M = 20	1.27	0.95 to 1.71	0.104
[Stata: mim: glm, fam(Poisson) link(log) vce(robust)]				
PP population				
Sensitivity analysis: (PP population[a,c])	195	1.14	0.80 to 1.63	0.4684
[Proc glimmix, dist = bin link = log]				

M, number of data sets created in the multiple imputation analysis.
a Adjusted for baseline severity (one B-type ear or both), age and sex, and PCT.
b Multiple imputation of all missing data using baseline variables: use of antibiotics, eczema, hay fever, asthma, age, sex, baseline severity, baseline OMQ-14 and follow-up OMQ-14 weighted scores. Twenty imputed data sets were created using Stata version 13 and the ice and mim functions. The multiple imputation model was run using Stata glm (generalised linear model) with options fam(Poisson) link(log) vce(robust).
c $n = 24$ excluded because of < 70% compliance; $n = 15$ excluded, visit outside allowable visit window (autoinflation); $n = 17$ excluded, visit outside allowable visit window (standard care).

A further multiple imputation analysis was specified in the statistical plan, which proposed imputation for only those participants in whom data were missing for reasons that were not clinical (wax, perforation). This applied to only six participants, so this analysis was not performed.

Subgroup analyses

Pre-specified subgroups analyses of age (< 6.5 years vs. ≥ 6.5 years), severity (one vs. two B-type ears at baseline), OMQ-14 standardised total score (< 0 or ≥ 0) and sex were conducted on the primary outcome. In all cases no differences in treatment effects between subgroups were found. The *p*-values for the interaction term (treatment by subgroup) in the model ranged from 0.25 to 0.50. Although the interaction terms are not significant, they are of sufficient clinical interest to be considered further as additional (not pre-specified) secondary analyses (see *Additional secondary analyses* and *Tables 24–29*).

Secondary outcomes

Proportion of children showing clearance/resolution of at least one type B tympanogram (effusion) back to normal A/C1 pressures at 3 months

The resolution of at least one B-type ear at 3 months was analysed in the same way as the 1-month primary end point. There were 108 children with resolution of at least one B-type ear at 3 months. At 3 months, those in the autoinflation group were 37% more likely to have resolution of at least one B-type ear (RR 1.37, 95% CI 1.03 to 1.83; $p = 0.0283$) (*Table 15*).

Proportions of children's ears showing resolution of a type B tympanogram back to A/C1 normal pressures at 1 and 3 months

An analysis of each ear separately was conducted, adjusting for the correlation between ears from the same child using generalised estimating equations (*Table 16*). Results were very similar to the main per-child analyses.

TABLE 15 Summary of the main tympanometric outcomes at 1 and 3 months

Tympanometric resolution in children of at least one affected type B ear	*n*	Standard care, *n/N* (%) resolved	Autoinflation, *n/N* (%) resolved	NNT	Adjusted RR (95% CI)	*p*-value
1-month analysis[a]	263	47/132 (35.6)	62/131 (47.3)	9	1.36 (0.99 to 1.88)	0.06
3-month analysis[b]	245	46/120 (38.3)	62/125 (49.6)	9	1.37 (1.03 to 1.83)	0.03

a Adjusted for baseline severity (one or two B-type ears), age and sex, and PCT.
b Adjusted for baseline severity (one or two B-type ears), age and sex (not adjusted for centre effects because of non-convergence).

TABLE 16 Per-ear resolution at 1 and 3 months

Tympanometric resolution in B-type ears	*n*	Standard care, *n/N* (%) resolved	Autoinflation, *n/N* (%) resolved	Adjusted RR (95% CI)	*p*-value
1-month analysis[a,b]	375 B-type ears/ 263 children	52/187 (28)	73/188 (39)	1.38 (1.01 to 1.87)	0.0420
3-month analysis[a,b]	348 B-type ears/ 245 children	52/166 (31)	74/182 (41)	1.41 (1.5 to 1.88)	0.0226

a Adjusted for baseline severity (one or two B-type ears), age and sex (not adjusted for centre effects because of non-convergence).
b Generalised estimating equation model adjusts for correlation between ears for each child.

Tympanometric deterioration

There were 92 A- or C1-type ears at baseline for which valid tympanograms were also available at 1 month (*Table 17*). At 1-month follow-up, three A-type ears had deteriorated to B-type ears (one in the standard care group and two in the autoinflation group). Six of the C1-type ears had deteriorated to become B-type ears (four in the standard care group and two in the autoinflation group). Owing to the small number of deteriorations there was no further analysis on this end point.

OMQ-14 impact measure

Table 18 displays summary statistics for baseline and follow-up (3-month) standardised OMQ-14 scores. Higher (more positive) scores represent worse outcomes. The average change from baseline in the standard care group was a decrease of 0.2 points, compared with a decrease of 0.7 points in the autoinflation group ($p < 0.0001$).

A mean change in baseline score of –0.69 points (SD 0.84 points) at 3 months in the treated arm represents a large improvement.

At 3 months, the adjusted mean change from baseline in the standardised OMQ-14 total scores was greater in the autoinflation than in the routine care arm (*Table 19*). The difference between groups was –0.42 (95% CI –0.63 to –0.22) points. This score difference represents an adjusted effect size of 0.48 (of a SD; $p < 0.0001$) favouring the intervention (*Figure 6*).

TABLE 17 Tympanometric deterioration of A- and C1-type ears at 1 month

Group	Ears with no deterioration	Ears which deteriorated	Total
Standard care	38	5	43
Autoinflation	45	4	49
Total	83	9	92

TABLE 18 Summary statistics for standardised OMQ-14 scores

Group	Time point	*n*	Number missing	Mean	SD	Minimum	Maximum
Standard care	Baseline	153	7	–0.04	0.95	–1.93	2.90
	3 months	121	39	–0.37	1.06	–2.15	3.06
	Change from baseline	121	39	–0.21	0.90	–3.11	1.90
Autoinflation	Baseline	153	7	–0.07	1.00	–1.81	2.88
	3 months	127	33	–0.70	1.01	–2.12	3.11
	Change from baseline	126	34	–0.69	0.84	–2.58	1.44

Note
A lower/more negative score indicates a better outcome.

TABLE 19 Change in standardised OMQ-14 scores

Group	*n*	Adjusted mean[a] change from baseline	95% CI	Mean difference	95% CI	*p*-value
Standard care	121	–0.22	–0.40 to –0.04			
Autoinflation	126	–0.64	–0.81 to –0.47	–0.42	–0.63 to –0.22	< 0.001

a Adjusted for sex, age, centre (PCT), baseline values and baseline severity.
A lower/more negative score indicates a better outcome.

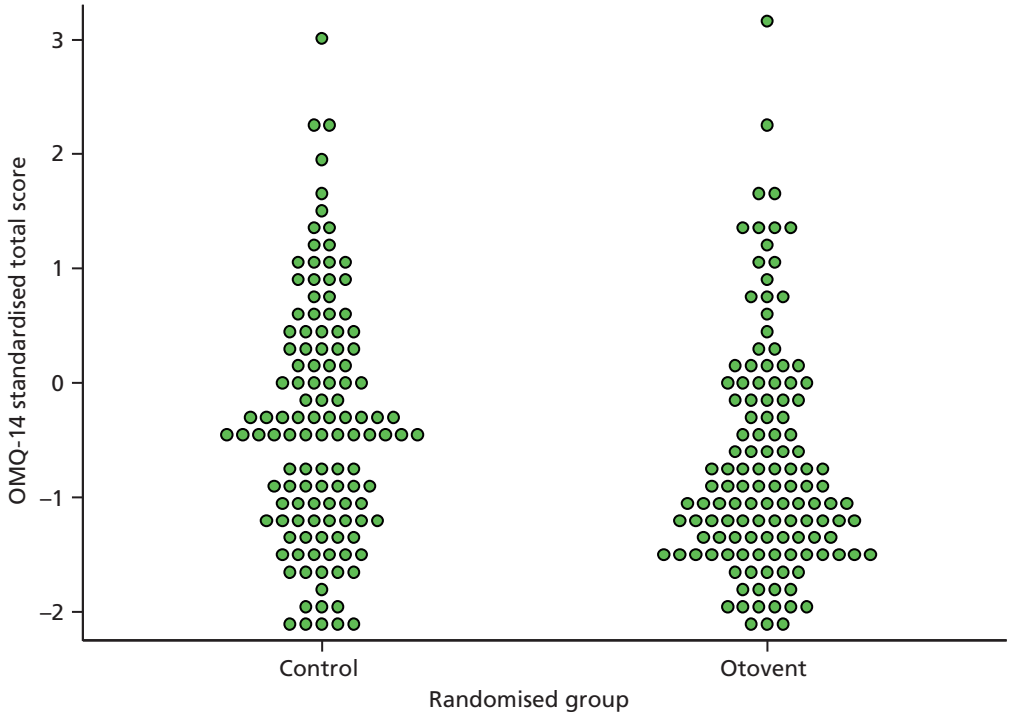

FIGURE 6 Standardised OMQ-14 scores at the 3-month follow-up. A lower/more negative score indicates a better outcome.

Main clinical diary symptoms

Days during which parents reported their child had hearing loss, earache, sleep disturbance or problems concentrating, and days requiring pain relief and days off school were summarised in accordance with the statistics plan (to avoid multiple outcomes) as days with any problem (*Table 20*). Overall, children in the autoinflation arm had fewer days/weeks with any symptom/problem at 1 month (OR 0.66, 95% CI 0.41 to 1.05; $p = 0.08$) and at 3 months (OR 0.58, 95% CI 0.37 to 0.90; $p = 0.02$).

Additional symptoms

Additional potentially adverse symptoms are reported in *Table 21*. See also *Adverse events*, which describes how the study collected symptoms from the reported adverse events sheets.

TABLE 20 Parent-reported days/weeks with symptoms

Days reporting one or more symptoms	Class	Standard care, *n* (%)	Autoinflation, *n* (%)	OR	95% CI	*p*-value[a]
0–1 month: days reporting one or more symptom[b]	None	9 (2.8)	18 (5.6)	0.658	0.413 to 1.048	0.0778
	1–7 days	47 (14.7)	49 (15.3)			
	≥ 8 days	82 (25.6)	69 (21.6)			
	Missing	22 (6.9)	24 (7.5)			
1–3 months: days reporting one or more symptom[b]	None	4 (1.3)	9 (2.8)	0.579	0.372 to 0.902	0.0157
	1–7 days	29 (9.1)	30 (9.4)			
	8–28 days	57 (17.8)	73 (22.8)			
	≥ 29 days	49 (15.3)	27 (8.4)			
	Missing	21 (6.6)	21 (6.6)			

a Adjusted for age and sex.
b Hearing loss, earache, sleep disturbance, problems concentrating, days requiring pain relief and days off school.

TABLE 21 Additional recorded diary symptoms

OME diary question	1-month totals				3-month totals			
	Weeks with symptoms	Standard care, *n* (%)	Autoinflation, *n* (%)	*p*-value[a]	Weeks with symptoms	Standard care, *n* (%)	Autoinflation, *n* (%)	*p*-value[a]
Has your child been clumsy/ off-balance?	Missing	22 (6.9)	24 (7.5)		Missing	21 (6.6)	21 (6.6)	
	None	81 (25.3)	101 (31.6)	0.0259	None	68 (21.3)	92 (28.8)	0.0073
	1 week	14 (4.4)	13 (4.1)		< 1 month	31 (9.7)	29 (9.1)	
	2 weeks	13 (4.1)	10 (3.1)		4–7 weeks	23 (7.2)	10 (3.1)	
	3 weeks	8 (2.5)	5 (1.6)		≥ 8 weeks	17 (5.3)	8 (2.5)	
	4 weeks	22 (6.9)	7 (2.2)					
Has your child been unwell/ had a temperature?	Missing	23 (7.2)	24 (7.5)		Missing	21 (6.6)	21 (6.6)	
	None	56 (17.5)	61 (19.1)	0.8345	None	33 (10.3)	35 (10.9)	0.6967
	1 week	45 (14.1)	45 (14.1)		< 1 month	79 (24.7)	78 (24.4)	
	2 weeks	20 (6.3)	19 (5.9)		4–7 weeks	22 (6.9)	24 (7.5)	
	3 weeks	9 (2.8)	5 (1.6)		≥ 8 weeks	5 (1.6)	2 (0.6)	
	4 weeks	7 (2.2)	6 (1.9)					
Has your child had a runny nose?	Missing	23 (7.2)	24 (7.5)		Missing	21 (6.6)	21 (6.6)	
	None	43 (13.4)	25 (7.8)	0.0707	None	22 (6.9)	10 (3.1)	0.0201
	1 week	25 (7.8)	33 (10.3)		< 1 month	60 (18.8)	59 (18.4)	
	2 weeks	25 (7.8)	24 (7.5)		4–7 weeks	30 (9.4)	49 (15.3)	
	3 weeks	23 (7.2)	21 (6.6)		≥ 8 weeks	27 (8.4)	21 (6.6)	
	4 weeks	21 (6.6)	33 (10.3)					

continued

TABLE 21 Additional recorded diary symptoms (*continued*)

OME diary question	1-month totals				3-month totals			
	Weeks with symptoms	Standard care, *n* (%)	Autoinflation, *n* (%)	*p*-value[a]	Weeks with symptoms	Standard care, *n* (%)	Autoinflation, *n* (%)	*p*-value[a]
Has your child had a blocked nose/been snoring?	Missing	23 (7.2)	24 (7.5)		Missing	21 (6.6)	21 (6.6)	
	None	37 (11.6)	31 (9.7)	0.2211	None	21 (6.6)	14 (4.4)	0.1436
	1 week	19 (5.9)	17 (5.3)		< 1 month	38 (11.9)	43 (13.4)	
	2 weeks	9 (2.8)	21 (6.6)		4–7 weeks	29 (9.1)	42 (13.1)	
	3 weeks	20 (6.3)	17 (5.3)		≥ 8 weeks	51 (15.9)	40 (12.5)	
	4 weeks	52 (16.3)	50 (15.6)					
Has your child had any nosebleeds?	Missing	23 (7.2)	24 (7.5)		Missing	21 (6.6)	21 (6.6)	
	None	124 (38.8)	121 (37.8)	0.3687	None	114 (35.6)	114 (35.6)	0.5546
	1 week	10 (3.1)	9 (2.8)		< 1 month	24 (7.5)	22 (6.9)	
	2 weeks	2 (0.6)	3 (0.9)		4–7 weeks	0	2 (0.6)	
	3 weeks	0	3 (0.9)		≥ 8 weeks	1 (0.3)	1 (0.3)	
	4 weeks	1 (0.3)	0					

a Adjusted for age and sex.

Compliance

Of the 130 parents recorded, 116 (89%) reported the use of autoinflation as 'most' or 'all of the time' during the first month of treatment, consistent with the daily compliance charts. This level of compliance appears to be maintained in those continuing treatment up to 3 months (68/85, 80%) (*Table 22*). *Figures 7* and *8* show median comparator estimates for the two methods used to assess compliance (diary sticker charts and parental report).

TABLE 22 Parent-reported compliance with autoinflation

Parent reported how often the child performed autoinflation	Diary compliant days at month 1[a]			Diary compliant days at months 2–3[a]		
	n	Median	Range	*n*	Median	Range
Not at all	1	0	0–0	1	27	27–27
Some of the time	11	9	0–19	14	20.5	0.0–34.0
Most of the time	63	26	3–28	47	52	0–56
All of the time	53	28	0–28	21	56	33–56
Missing	2	13	5–21	2	37	18–56
Overall	130	26	0–28	85	51	0–56

a Two or more uses per day.

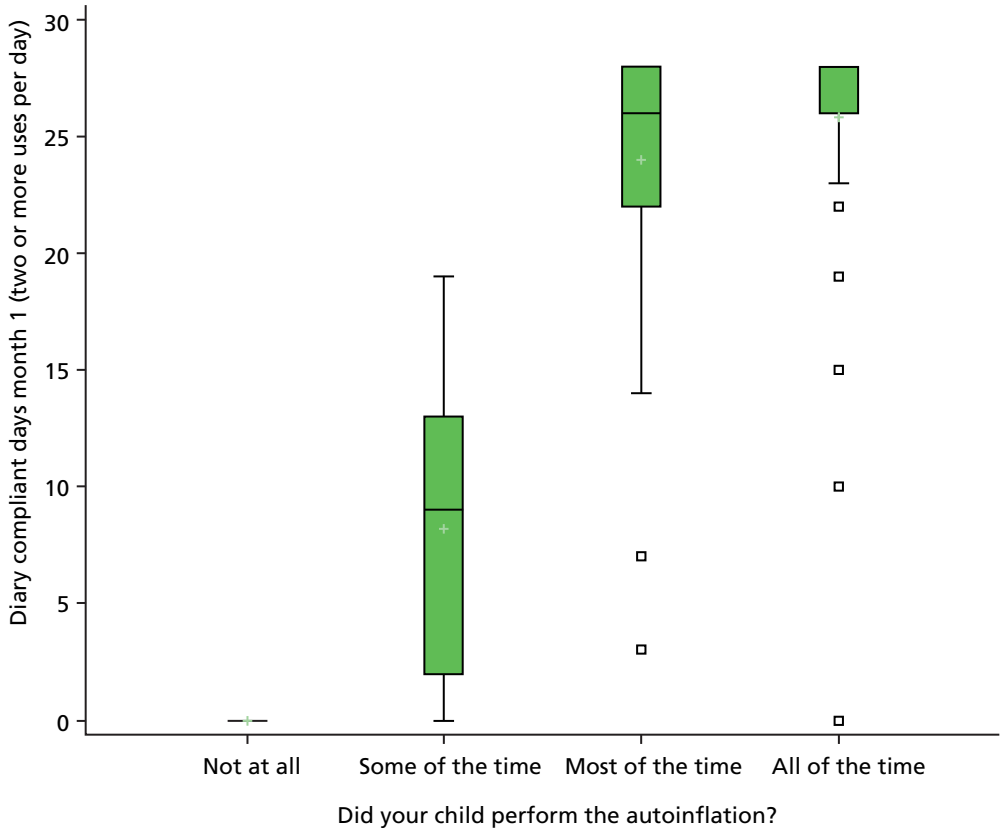

FIGURE 7 Compliance for months 0–1 (diary assessment vs. parental report of compliance).

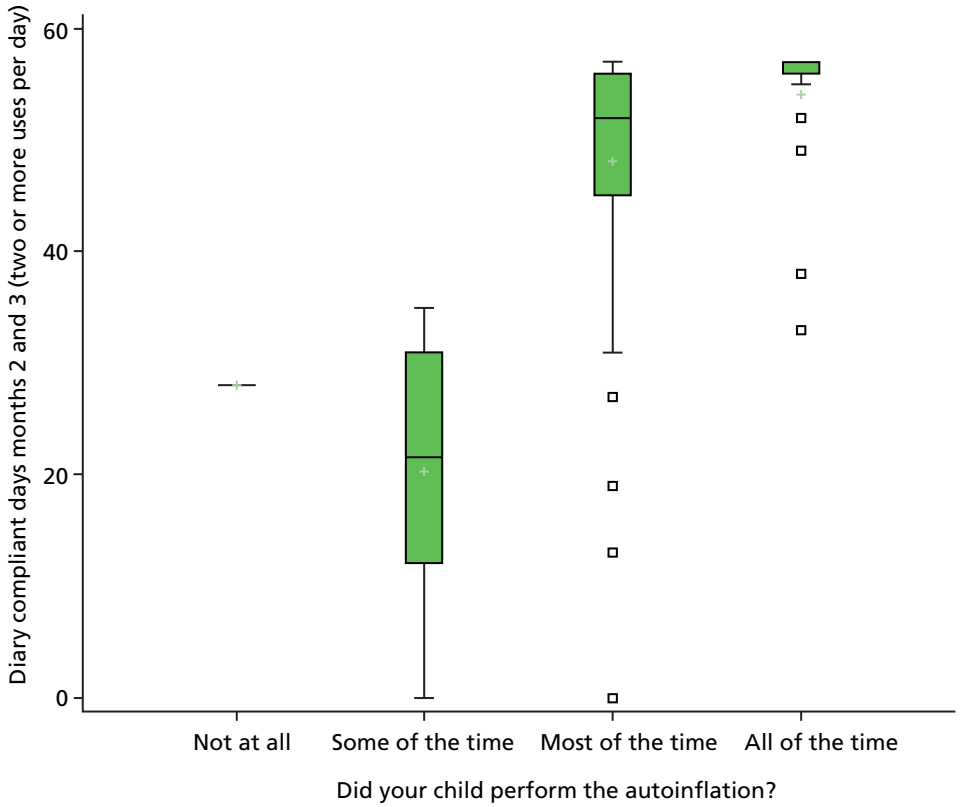

FIGURE 8 Compliance for months 1–3 (diary assessment vs. parental report of compliance).

Adverse events

As there were no previously reported adverse events for autoinflation, apart from anecdotal otalgia, the events recorded here are otherwise biased towards overinclusivity, and some overlap with the additional symptoms reported in *Table 21*. There was very little difference between treatment arms in terms of numbers of children with a nosebleed (15% vs. 14%), but there were more reported RTIs in the treatment group (18% vs. 13% of children, 37 vs. 18 episodes). Most of the RTIs were classified, however, as mild afebrile rhinorrhoea. Eight children in the autoinflation arm (compared with two in routine care) reported otalgia (*Table 23*). One 8-year-old child in the autoinflation arm was hospitalised with mild/early mastoiditis on day 10 of treatment and made a full recovery after treatment with intravenous antibiotics.

No bacteriology was available to confirm the cause. Clinical details of relevance were obtained in full and revealed that the child had been investigated by a paediatrician for recurrent RTIs in the previous 12 months. The case was reviewed independently by the DMEC (see *Appendix 7*). It was noted that no previous cases of mastoiditis had been reported with the use of Otovent, a device available over the counter in the UK and abroad, and no cases had been reported in any of the previous trial literature (≈500 receiving autoinflation). The DMEC did a full risk assessment and advised that it was safe to continue with the study.

TABLE 23 Adverse events (based on completed adverse events report forms)

	Standard care ($n = 160$)		Autoinflation plus standard care ($n = 160$)	
Adverse event	Events, *n*	Affected children, *n* (%)	Events, *n*	Affected children, *n* (%)
Nosebleed	26	24 (15)	26	22 (14)
URTI	6	6 (4)	20	13 (8)
Unspecified RTI	4	4 (3)	9	9 (6)
Lower RTI	4	4 (3)	2	2 (1)
AOM	4	4 (3)	6	5 (3)
Otalgia	2	2 (1)	8	7 (4)
Headache	–	–	2	2 (1)
Hay fever	–	–	1	1
Serious adverse event				
Hospitalisation[a]	1	1 (1)	1	1 (1)

a Renal angle pain (standard care), acute mastoiditis (autoinflation).

Additional secondary analyses

Tables 24–29 deal in more detail with specified subgroups and have been included because of clinical importance and interest to the general literature. The analyses are not sufficiently powered and show a number of non-significant *p*-values for each headed subgroup. Details of the overlapping CIs between the two study arms for resolution rates (primary outcome) are also shown.

We have also, for reasons of clinical interest, added to this section the pre-baseline symptom (history) predictors of the finding of at least one type B tympanogram in the screened child. A univariate analysis was performed on all the parent-listed ear symptom/concerns items in the previous 3 months and those items that remained significant (*Table 30*) were then added in a stepwise multivariate analysis to derive a receiver operator characteristic (ROC) curve (*Figure 9*).

TABLE 24 Primary outcome by baseline severity

	Bilateral		Unilateral	
Randomised group	No resolution	Resolution	No resolution	Resolution
Autoinflation, *n* (%)	29 (48.33)	31 (51.67)	40 (56.34)	31 (43.66)
Standard care, *n* (%)	39 (65.00)	21 (35.0)	46 (63.89)	26 (36.11)
RR (95% CI)	1.48 (0.97 to 2.25)		1.21 (0.81 to 1.81)	

$p = 0.5048$ for comparison between two treatment effects (RR 1.48 vs. 1.21).

TABLE 25 Primary outcome by sex

	Male		Female	
Randomised group	No resolution	Resolution	No resolution	Resolution
Autoinflation, *n* (%)	31 (46.97)	35 (53.03)	38 (58.46)	27 (41.54)
Standard care, *n* (%)	44 (65.67)	23 (34.33)	41 (63.08)	24 (36.92)
RR (95% CI)	1.54 (1.03 to 2.31)		1.125 (0.730 to 1.720)	
$p = 0.2912$ for comparison between two treatment effects (RR 1.540 vs. 1.125).				

TABLE 26 Primary outcome by age

	Age ≥ 6.5 years		Age < 6.5 years	
Randomised group	No resolution	Resolution	No resolution	Resolution
Autoinflation, *n* (%)	13 (41.94)	18 (58.06)	54 (55.10)	44 (44.90)
Standard care, *n* (%)	18 (64.29)	10 (35.71)	65 (63.73)	37 (36.27)
RR (95% CI)	1.63 (0.91 to 2.90)		1.24 (0.88 to 1.74)	
$p = 0.4267$ for comparison between two treatment effects (RR 1.63 vs. 1.24).				

TABLE 27 Primary outcome by standardised OMQ-14 score at baseline

	OMQ-14 score of ≥ 0		OMQ-14 score of < 0	
Randomised group	No resolution	Resolution	No resolution	Resolution
Autoinflation, *n* (%)	28 (49.12)	29 (50.88)	41 (56.94)	31 (43.06)
Standard care, *n* (%)	36 (67.92)	17 (32.08)	46 (61.33)	29 (38.67)
RR (95% CI)	1.59 (0.99 to 2.53)		1.11 (0.75 to 1.64)	
$p = 0.2556$ for comparison between two treatment effects (RR 1.59 vs. 1.11).				

TABLE 28 Primary outcome by recorded related GP visits for hearing, snoring, educational or behavioural concerns

	No GP visits		At least one GP visit	
Randomised group	No Resolution	Resolution	No Resolution	Resolution
Autoinflation, *n* (%)	54 (55.10)	44 (44.90)	15 (45.45)	18 (54.55)
Standard care, *n* (%)	66 (68.75)	30 (31.25)	19 (52.78)	17 (47.22)
RR (95% CI)	1.44 (0.99 to 2.08)		1.15 (0.73 to 1.84)	
$p = 0.4719$ for comparison between two treatment effects (RR 1.44 vs. 1.15).				

TABLE 29 Primary outcome by season

	Spring: March–May		Summer: June–August		Autumn: September–November		Winter: December–February	
Randomised group	No resolution	Resolution	No resolution	Resolution	No resolution	Resolution	No resolution	Resolution
Autoinflation, *n* (%)	29 (47.54)	32 (52.46)	4 (57.14)	3 (42.86)	16 (69.57)	7 (30.43)	20 (50.00)	20 (50.00)
Standard care, *n* (%)	38 (61.29)	24 (38.71)	4 (50.00)	4 (50.00)	17 (73.91)	6 (26.09)	26 (66.67)	13 (33.33)
RR (95% CI)	1.36 (0.91 to 2.01)		0.86 (0.29 to 2.58)		1.167 (0.46 to 2.94)		1.50 (0.87 to 2.58)	
$p = 0.8285$ for comparison across all treatment effects.								

TABLE 30 Clinical history predictors of children with type B tympanogram(s)

Baseline-reported symptom	Univariate analysis (95% CI)	Multivariate OR (95% CI)
A prolonged or bad cold, cough or chest infection	1.80 (1.23 to 2.64)	
Appears to be lip reading	2.18 (1.51 to 3.15)	
An earache	1.98 (1.51 to 3.15)	
Not doing as well at school as expected	1.54 (1.13 to 2.59)	
Often mishears what is said	2.55 (1.85 to 3.51)	1.79 (1.26 to 2.56)
Hearing loss is suspected by anyone	2.41 (1.83 to 3.17)	
Snores, blocked nose or poor sleep	1.57 (1.17 to 2.10)	
Says 'eh what?' or 'pardon' a lot	2.14 (1.52 to 3.02)	
Needs the television turned up	2.32 (1.76 to 3.04)	1.64 (1.22 to 2.23)
Any suspected ear problem	2.74 (2.05 to 3.65)	2.04 (1.48 to 2.79)
May be irritable or withdrawn	1.28 (0.95 to 1.72)	
Speech behind other children	1.14 (0.81 to 1.59)	
Noises in ear/dizzy	1.32 (0.96 to 1.81)	

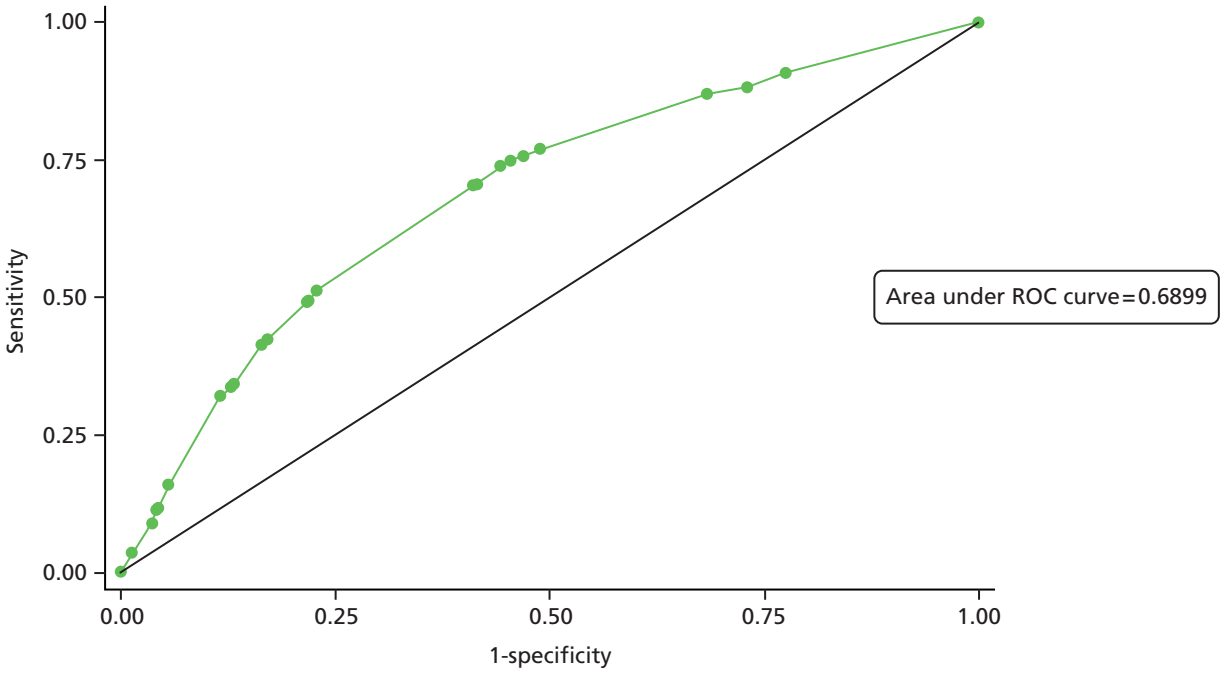

FIGURE 9 Area under the ROC curve based on independent historical variables.

Meta-analysis for research in context

A meta-analysis with trials identified in the recent Cochrane review[35] using similar outcomes at 1 month (ear-based analysis B to A/C1) favoured autoinflation (RR 1.61, 95% CI 1.26 to 2.06) (*Figure 10*). When the pilot study was combined with the main study as per the statistical plan, the primary care setting studies, when pooled, found a RR of 1.37 (95% CI 1.00 to 1.87) (*Figure 11*).

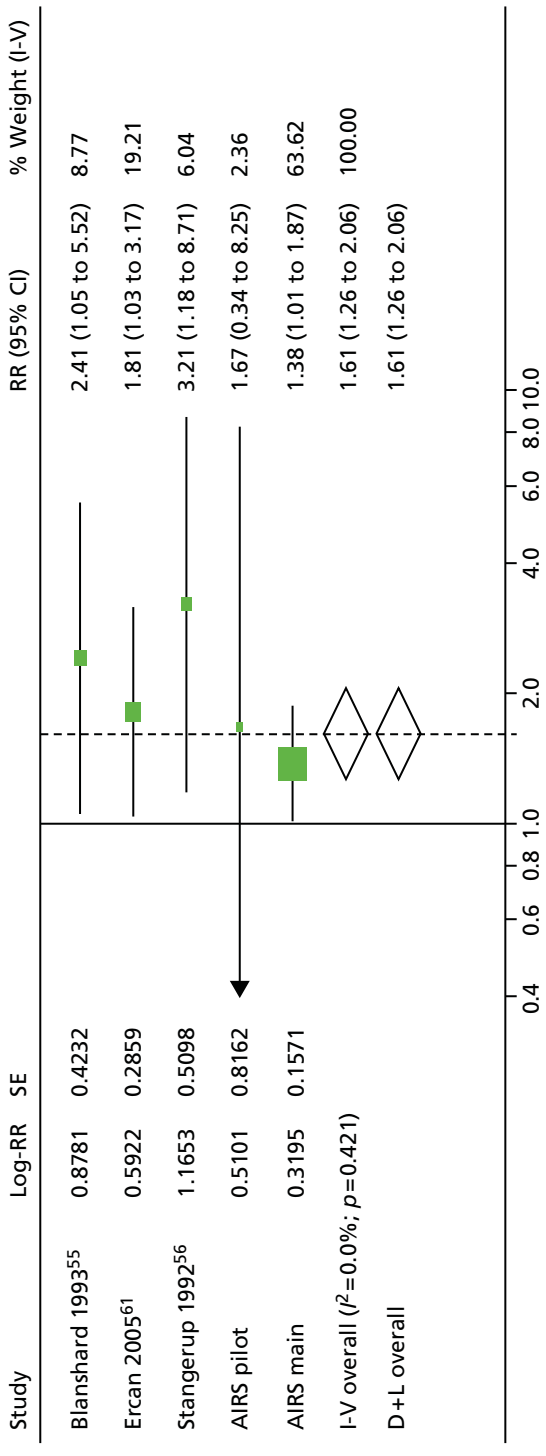

FIGURE 10 Meta-analysis of 1-month outcomes (ear-based analysis). AIRS, AutoInflation Randomised Study; D+L, DerSimonian and Laird method; I-V, inverse variance method; SE, standard error.

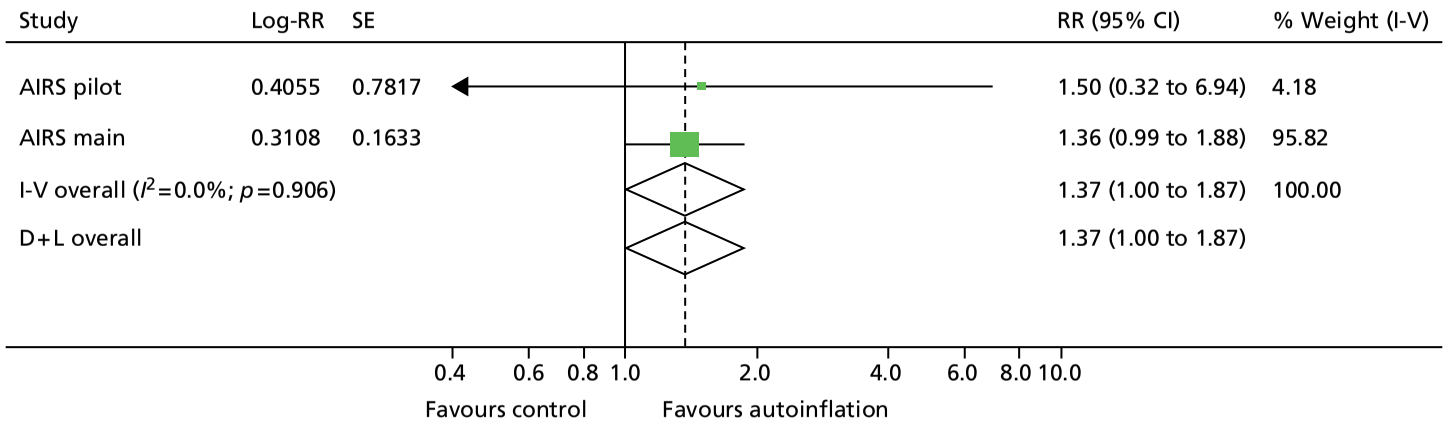

FIGURE 11 Meta-analysis primary care studies (per-child analysis) at 1 month. AIRS, AutoInflation Randomised Study; D + L, DerSimonian and Laird method; I-V, inverse variance method; SE, standard error.

Chapter 5 Health economic analysis

Introduction

The AutoInflation Randomised Study (AIRS) was designed to estimate the clinical effectiveness and cost-effectiveness of autoinflation alongside standard care compared with standard care alone in children with OME in primary care. An economic analysis was part of the design of the study. Data on resource use and health-related QoL using the HUI3[76,77,89] were collected during the trial. Outcomes were expressed both as cost per QALY gained and as cost per additional proportion of tympanic resolution of the intervention compared with standard care. This section reports that analysis.

Methods

The economic evaluation was taken from both the NHS and a Personal Social Services perspective. The baseline analysis was at 3 months. Resource usage beyond 3 months and the effects of including travel costs and those due to parents' time off work were explored in scenario analysis.

Data collection

Resource usage data were extracted at 6 months after recruitment by study nurses through searching electronic records. A restricted set of resource use data were also extracted at 12 months focusing on hospital admissions related to otitis media. This was because grommet insertion, the most common specialist treatment, is often delayed by over 6 months after presentation. HUI3 forms were completed by patients at baseline, at 1 month and at 3 months. At 3 months after recruitment, parents completed an extra questionnaire on travel costs and time off work due to ear-related illness of their children.

Cost estimation

Resource use costs

Resource use included primary care consultations, prescribed medication, all otitis-related outpatient referrals, referrals for audiology, speech therapy or to community health-care professionals and any ear-related hospitalisations.

Medications

Medications recorded related to otitis media included antibiotics, decongestants and antihistamines, and analgesics. The names of medication, dosage and days of use were recorded. We used the pack price in costing all medications on the basis that this reflected the real costs of NHS resource use. The number of packs was estimated and costed based on actual duration. If no data were available on the duration of medications use was available, then one pack was assumed. The unit costs of medications were obtained from data published by the *British National Formulary* in September 2012 (*Table 31*).[90]

Primary care consultations and secondary care costs

The unit costs of primary and secondary care consultations used were those published by Personal Social Services Research Unit at 2011–12 prices (see *Table 25*).[91] The Healthcare Resource Group costing applicable to study patients was based on their diagnoses, minor ear procedures, minor nose procedures and ENT outpatient costs (CZ12U).

TABLE 31 Unit costs of medication (2011–12 prices)

Name	Contents	Formulation	Pack volume	Pack/dose units	Price/pack
Amoxicillin (Amoxil®, GlaxoSmithKline)	1 bottle	Suspension	100	ml	£1.13
Cefalexin	28	Tablets	250	mg	£1.90
Clarithromycin (Klaricid®, Abbott Healthcare)	14	Tablets	250	mg	£1.89
Co-amoxiclav (Augmentin®, GlaxoSmithKline)	1 bottle	Suspension	100	ml	£1.94
Erythromycin	28	Tablets	250	mg	£23.43
Ofloxacin (Exocin®, Allergan)	1	Eye drops	5	ml	£2.17
Otomize spray (Cofradex®, Sanofi-aventis)	1	Ear spray	5	ml	£3.50
Penicillin V Elixir	28	Tablets	250	mg	£1.40
Ciprofloxacin (Ciloxan®, Alcon)	1	Eye ointment	3.5	g	£5.22
Ciprofloxacin drops (Ciloxan®, Alcon)	1	Eye drops	5	ml	£4.70
Betamethasone (Betnesol®, RPH)	1 ampoule	Ampoule	4	mg	£1.22
Trimethoprim	14	Tablets	200	mg	£0.98

Intervention costs

The intervention cost was based on the price charged by the company supplying Otovent packs to the NHS and the time required for training children in its use. The 2014 price to the NHS was £4.90 for one pack of Otovent (tube and five balloons). All patients in the intervention group were given one pack of the Otovent. However, if resolution was not achieved at 1 month, a second pack of Otovent was given to those patients. One consultation of 4 minutes with a practice nurse comprised training in the use of the Otovent. The dispensing cost was included (*Table 32*).

Quality of life

Self-completed questionnaires using the HUI3 were recorded at baseline, 1 month and 3 months during the trial. The data in eight categories were used to estimate utility scores for each individual child. The mapping algorithm and score functions were purchased from Health Utilities Inc. The algorithms map data from the 17-item interviewer-administered questionnaire to each of eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain) of the HUI3 classifications. Utility scores for each patient were calculated based on these algorithms.

Analysis

The economic analysis was conducted using patient-specific resource use and QoL data. The time frame was 3 months for the primary outcome, but for 12 months a restricted data set was collected on resource use. The base case for the economic analysis (equivalent to the primary analysis of the main study) was at 3 months for both outcomes and costs. The data on resource use at 12 months were compared between arms with a focus on hospitalisations.

Accumulated total costs per patient were calculated by the sum of the products of resource use items and the associated unit costs, aggregated over the study period. QALYs for each patient were calculated according to the utility scores derived from HUI3 at baseline, 1 and 3 months using the area under the curve, and adjusted baseline difference in QoL scores, using the mean value between utility scores at baseline.

TABLE 32 Unit costs of primary and secondary care consultations (2012–13 prices)

Resource use item	Unit cost and source
Intervention cost (device and training on how to use)	Average 4 minutes per patient training with nurse (£52 per hour) = £3.47. Cost of device (4-week course) = £6.90 including dispensing costs
Practice nurse telephone call	Cost of standard nurse telephone call (6 minutes, at £40 per hour), including qualifications Source: PSSRU 2013 (table 10.6)[91] = £4.00
Practice nurse consultation in GP practice	Cost of standard face to face nurse consultation (£52 per hour), including qualifications Source: PSSRU 2013 (table 10.6)[91] = £13.43
GP consultation	Consultation lasting 11.7 minutes, including qualifications and direct care staff costs Source: PSSRU 2013 (table 10.8b)[91] = £45
GP home visit	Out-of-surgery visit, GP Source: PSSRU 2013 (table 10.8b)[91] = £114
Out-of-hours GP consultation	Out-of-hours benchmark, includes overheads = £61.14 Source: Primary Care Foundation, 2013[92]
ENT outpatient attendance	Paediatric ENT outpatient attendance, service code 215 = £95
Ear-related inpatient cost, paediatrics	Minor ear procedures, elective inpatients, 18 years and under paediatric ENT CZ08T, service code 215 = £1295 Source: NHS Reference Costs 2013[93]
Adenoidectomy inpatient hospital cost, paediatrics	Minor nose procedures, elective inpatients, 18 years and under CZ12U, service code 215 = £1472 Source: NHS Reference Costs, 2013[93]
Non-ENT-related outpatient visit	Paediatric outpatient = £187, service code 420 Source: NHS Reference Costs, 2013[93]

PSSRU, Personal Social Services Research Unit.

Missing data

Missing data in QoL scores derived from HUI3 were assumed to be equal to the mean for each treatment group by time point.

The mean cost per patient and QALYs associated with the intervention and standard care group were calculated and the differences between them evaluated in accordance with ITT principle. The bias-corrected bootstrap method was used to estimate mean costs, QALYs and the incremental cost-effectiveness ratio (ICER) with the associated 95% CI. Uncertainty around the costs and effectiveness estimates was illustrated using a scatterplot with a confidence ellipse. Cost-effectiveness acceptability curves were drawn to show the probability of the intervention being cost-effective given the level of willingness to pay per QALY gained.

Although the base-case analysis used ITT, a cost-effectiveness analysis was carried out on patients for whom clinical outcome data were available at 3 months (120 and 125 patients in the intervention and standard care arms respectively). The analyses were conducted in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The NHS costs at 3 months showed no statistically significant differences between arms (*Tables 33* and *34*). The mean cost per patient at 3 months was £17.61 (95% CI £10.42 to £24.81) for the routine care arm, compared with £31.94 (95% CI £23.69 to £40.19) for the Otovent plus routine care arm. The higher mean cost in the intervention arm was almost entirely caused by the cost of the intervention at £14.22. Only small differences were found between arms in use of the other resource headings.

TABLE 33 Mean NHS costs per patient at 3 months

Intervention	*n*[a]	Mean	SD	95% CI[b]
Standard care group				
Total cost	132	£17.613	£41.771	£10.42 to £24.805
Primary care visits	28	£53.97	£33.958	£40.802 to £67.137
Outpatient attendance	8	£95	0	
Medication	16	£3.358	£2.601	£1.972 to £4.743
Intervention	0			
Autoinflation group				
Total cost	131	£31.941	£47.733	£23.69 to £40.192
Primary care visits	31	£54.613	£44.956	£38.123 to £71.103
Outpatient attendance	5	£114	£42.485	£61.248 to £166.752
Medication	19	£3.046	£2.295	£1.94 to £4.152
Intervention	131	£14.224	£3.458	£13.627 to £14.822

a *n* for total cost refers to the number in each arm. *n* of rows below refer to the number of patients using that service. The mean total cost refers to the mean for each arm.
b Confidence limit is for the mean.

TABLE 34 Utility scores, changes from baseline and QALYs by arm

Utility scores	Standard care (95% CI) (*n* = 132)	Autoinflation (95% CI) (*n* = 131)
Utility score at baseline	0.781 (0.744 to 0.818)	0.758 (0.717 to 0.798)
Utility score at month 1	0.787 (0.747 to 0.828)	0.808 (0.768 to 0.847)
Utility score at month 3	0.843 (0.811 to 0.876)	0.846 (0.808 to 0.885)
Utility score changed from baseline at 1 month	0.006 (–0.03 to 0.042)	0.050 (0.015 to 0.084)
Utility score changed from baseline at 3 months	0.062 (0.025 to 0.1)	0.089 (0.05 to 0.127)
QALYs (adjusted baseline difference)	0.197 (0.188 to 0.205)	0.200 (0.191 to 0.209)

Quality of life

Utility scores at baseline, 1 month and 3 months and their changes from baseline at 1 month and 3 months are presented in *Table 34*. QALYs estimated from the HUI scores showed small differences between arms at baseline and at 1 and 3 months. The mean QALY gain was 0.197 (95% CI 0.188 to 0.205) in the control group and 0.200 (95% CI 0.191 to 0.209) in the intervention group. This small difference was not statistically significant.

Although the incremental difference in the primary outcome, tympanometric resolution of fluid, was statistically significant at 3 months, the difference in QALYs, although in the same direction, just missed statistical significance.

Mean incremental bootstrapped difference in QALYs, costs and ICERs (*Table 35*) put the ICER at £8463 (95% CI –£104,894 to £121,820). Although the QALY difference was not statistically significant, the bootstrapped cost difference was.

The incremental cost per case resolved, based on those for whom data were available, was £132 (95% CI –£2315 to £2333) (*Table 36*).

TABLE 35 Incremental costs, QALYs and cost per QALY

Outcomes	Mean	95% CI
QALY		
Standard care group	0.197	0.191 to 0.209
Autoinflation group	0.200	0.192 to 0.208
Difference	0.003	–0.010 to 0.020
Total cost		
Standard care group	£17.5	£10.5 to £24.9
Autoinflation group	£31.8	£24.2 to £39.9
Difference	£14.3	£3.5 to £25.2
ICER	£8463	–£104,894 to £121,820

TABLE 36 Cost per case resolved

Outcomes	Mean	95% CI[a]
Mean cost		
Standard care group	£19.02	£11.07 to £26.31
Autoinflation group	£26.79	£21.28 to £32.42
Difference	£7.78	–£1.29 to £17.61
Tympanometric resolution		
Standard care group	0.39	0.29 to 0.47
Autoinflation group	0.50	0.41 to 0.58
Difference	0.11	0.01 to 0.24
Incremental cost per case resolved	£132	–£2315 to £2333

a Confidence limit for mean.

Sensitivity analysis

The cost-effectiveness acceptibility curve (probabilistic sensitivity analysis) for the cost per QALY put the probability of the intervention being cost-effective at 50.1% and 50.2% at a willingness-to-pay threshold of £20,000 and £30,000 per QALY respectively (see *Figures 12* and *13*).

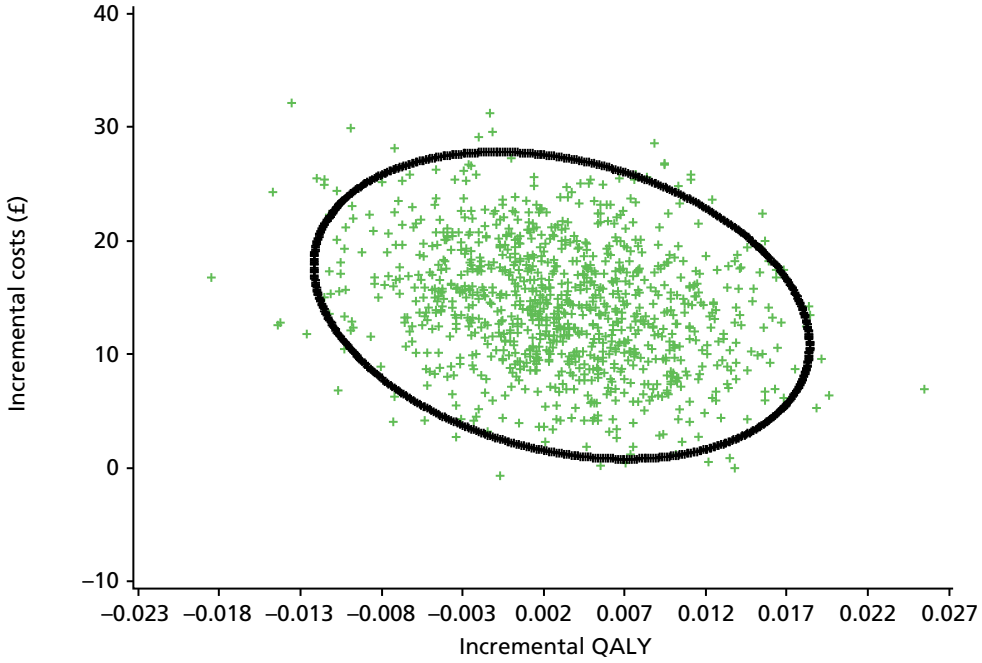

FIGURE 12 Scatterplot with 95% confidence ellipse. 95% confidence ellipse of difference in cost vs. QALY for Otovent vs. control.

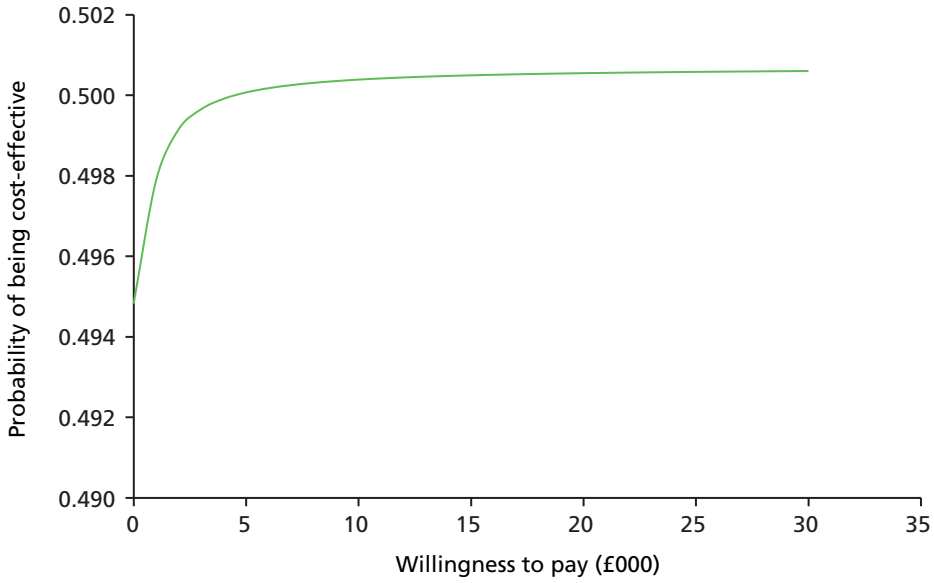

FIGURE 13 Cost-effectiveness acceptability curve.

Scenario analyses

Separate analysis explored resource use and cost at 12 months. This showed few hospitalisations in either arm and reflected the cost differences reported above at 3 months.

Another analysis explored privately borne costs regarding travel and parents' time off work. Only small differences were found in travel costs between arms. Similarly, few families reported time off work, with small differences between arms. Given the lack of difference in resource use between arms, this was as expected. Inclusion of these costs made minimal difference to the economic analyses reported above.

Full details of both above are available on request.

Discussion

The intervention improved outcomes at a low cost, leading to just over 50% probability of it being cost-effective at conventional cost per QALY thresholds. This analysis was based on ITT, a cost difference that was statistically significant when bootstrapped and a QALY difference that was not statistically significant.

The cost-effectiveness analysis was based on a smaller subset of patients for whom data were available. This showed a statistically significant difference in cases resolved at 3 months and put the cost per case resolved at £132.

The difference in mean cost was almost entirely caused by the cost of the intervention. The improved outcomes were not associated with any change in NHS service use, or with any privately borne costs. This may be because the improvement was insufficiently large to change patterns or service use, or it may be because of individual practitioners being reluctant to change their behaviours until evidence for an intervention is proven. Given that all unresolved children in the standard care arm were offered Otovent at 3 months as per the protocol (an ethical consideration), the effects are confounded beyond the end of the trial at 3 months.

Limitations of the CEA include:

- The duration was short, with outcomes followed up only to 3 months and with selected resource use up to 12 months. Follow-up on service use to 12 months showed no difference in hospitalisations for related conditions, the main one being grommet surgery (± adenoidectomy).
- HUI used US population weights. This was because of the greater experience of this instrument with children and its prior use in a similar study by the same team.[30] The QALY differences were reassuringly in the same direction as the primary outcome. Although US population weights were used, these are likely to be similar to those for the UK, as indicated by the similarity of US and UK weights for European Quality of Life-5 Dimensions.[94] The potentially beneficial effects of improvement in case resolution may over antibiotic prescribing have not been included.
- The potentially beneficial effects of improvement in case resolution over antibiotic prescribing have not been included.
- Although imputation was used in the clinical analysis of outcomes at 1 month, given that this made little difference to the results, a decision was made not to combine the methods of multiple imputation and bootstrapping.

Conclusions

The cost-effectiveness analysis based on the statistically significant difference in cases resolved puts the cost per case resolved at £132. Although the cost difference was not statistically significant, it was based almost entirely on the cost of the intervention.

The cost per QALY analysis showed the Otovent device to be just likely to be a cost-effective intervention. The uncertainty reflects the small and non-statistically significant difference in QALYs, a generic rather than condition-specific measure of outcome than the OMQ-14.

Chapter 6 Qualitative evaluation

Background

Autoinflation is a promising non-surgical treatment for OME, which has potential to improve natural resolution rates and QoL for children with OME-related concerns and symptoms, some of whom may be considered for ENT referral. The reliability of children inflating the nasal balloon and longer-term compliance with treatment has remained a concern regarding whether or not it could be a suitable treatment in primary care.[35] Although overall compliance has been assessed in the main trial, no previous qualitative work has been carried out with families or health-care professionals to explore facilitators and barriers to UK primary care management of OME, and the practicalities of use of autoinflation during this period.

This chapter reports a nested qualitative study, which is designed to inform the wider implementation of autoinflation in the primary care setting, including the monitoring process.

Objective

The qualitative study aims to explore the views and experiences of parents and practice nurses of both autoinflation and monitoring in primary care.

Methods

Participants and procedures

Participants were identified and recruited from general practices that participated in the main trial. A maximum variety sample[95] of practice nurses were invited to participate, including nurses from high- and low-recruiting practices, career RNs and practice nurses who undertake research alongside their normal duties. A maximum variety sample of parent participants ensured a range of child characteristics including age, sex, baseline severity of OME and GP practice location. This sampling was carried out to select a wide variety of 'information-rich cases', to obtain in-depth information about the issues relevant to the study.[95]

Interviews

Interviews were conducted either face to face or by telephone by a trained interviewer (JV), each lasting approximately 30 minutes. An interview guide was used to steer the interview while remaining sufficiently flexible to allow participants to raise issues that were important to them (see *Appendix 8*). Participants were asked about their views of screening and monitoring of glue ear in primary care, experiences of autoinflation including enablers and barriers to its use, and overall experiences of participating in AIRS. The interviews were digitally audio-recorded and transcribed verbatim, removing any identifiable data to ensure anonymity.

Analysis

Data were managed using NVivo 10 software and analysed using thematic analysis.[96] After initial familiarisation, the transcripts were systematically and comprehensively coded using open coding, a method of reducing the data while capturing the semantics and concepts of the data itself. The first three transcripts were coded by multiple coders and a coding framework agreed, improving the reliability of the study. Codes were refined into broad themes both inductively and guided by a priori knowledge of the topic area. Themes were then defined and described in relation to the research questions and existing literature.

Findings

Participants

A total of 33 participants took part in a research interview. Of these, 19 were practice nurses recruited from 18 GP practices across 10 former PCTs in the South West England, Thames Valley and Cheshire regions. Registered practice populations ranged from 3378 to 28,261, with the Index of Multiple Deprivation decile ranging from 6 to 10 (mid to low deprivation). Nurses variously described their employment status as practice nurses ($n = 11$), RNs ($n = 7$) and secondary care RNs ($n = 1$). The 14 parent participants were recruited from 10 practices in South West England and Thames Valley. All parents were the mothers, reflecting the usual carer who brought the child to the AIRS appointments.

Themes

Three key themes emerged from the analysis (*Table 37*). These themes are not an exhaustive account of the findings, but represent the major themes interpreted as relevant to the research question. Each theme is described in the following section and exemplar quotations are given to illustrate the subthemes.

Rationalising

This theme is defined as how parents seek information about OME and use their knowledge, experience and concerns to rationalise decisions about their child's management.

What parents knew about otitis media with effusion

Parents used a range of information including tacit knowledge, personal experience and information gathered from friends, family and health professionals to make sense of glue ear and understand the implications for their child. There was a mixed knowledge base, with some parents having a good insight into the causes and natural history of the condition, while others had not heard of glue ear before. Referencing to normal childhood behaviours, including ignoring instructions and misbehaviour, often meant that hearing impairment was not always recognised.

> *I mean I thought sometimes it was sort of a bit like a, you know, a normal child at that age, they don't want to answer you, sort of thing, they just ignore you anyway.*
>
> *Parent participant 13*

TABLE 37 Themes indentified in the analysis

Theme	Subtheme
Rationalising	What parents knew about OME
	Rationalising treatment decisions
Primary care management	Screening for OME
	Practice nurse as OME case manager
	Referral expectations
Engaging with monitoring and treatment	Interactions between nurses and families
	Compliance with autoinflation

Parents gathered information from various sources including the internet, friends and family, charitable sources, ENT departments and their GP practice. Nurses signposted parents to online information, often to the website Patient (www.patient.co.uk), which was considered a useful source. However, many parents relied solely on the information provided by their GP surgery, finding the information on the internet somewhat overwhelming.

> *We were given a lot of websites to look at and sometimes you can go information overload on them can't you?*
>
> *Parent participant 8*

Rationalising care decisions

Routine care [or active monitoring (AM)] was seen as a passive period of 'wait and see' rather than taking action, and this was unacceptable to some families. There was a general preference for non-surgical management of OME, although most parents would consider surgery if that was the only option or if the glue ear was considered to be particularly severe.

> *The grommets seem to be quite a good idea if . . . if, obviously, then if he had real bad problems.*
>
> *Parent participant 14*

Medical treatments such as antibiotics and steroids were not perceived by parents to be effective for OME, although there was some confusion with the diagnosis of AOM, for which antibiotics were seen as effective and acceptable. Autoinflation was described as a natural, holistic treatment that enables parents to feel that they are taking action, rather than waiting passively, as in the case with routine care.

> *Some parents don't want to stick pills into their children; they don't want to squirt stuff into their ear, they want to say, well, what else is there?*
>
> *Nurse participant 9*

Primary care management of otitis media with effusion

This theme is defined as how families and nurses understand the role of primary care in the early diagnosis and management of OME.

Screening for otitis media with effusion

Being invited for screening was viewed as positive by parents, although some nurses described certain parents as 'overly worried' rather than having real concerns about their child's hearing. Parents were advised one way or another if glue ear was present or absent and this helped with their future treatment or management decisions.

> *If it was – if it showed that they did have glue ear, possibly, the parents were quite relieved. I said, oh, you know, there could be – and they said, thank goodness, you know, there is something wrong.*
>
> *Nurse participant 12*

Practice nurse as case manager for otitis media with effusion

Nurses were sufficiently informed and skilled to screen children with tympanometry as part of the study, although some nurses reported anxiety with interpretation of the results. Nurses were considered by parents to be competent in screening and managing OME. They were described as accessible to families and, while knowing the whole family, could provide continuous, co-ordinated management in the wider family context. Nurses reported that it was feasible to provide screening in primary care, although workload management and financial constraints were suggested as potential barriers.

> *There's always a huge time pressure and more and more and stuff is being moved from hospital into general practice; we are all up-skilling all the time, so it would be a financial consideration.*
>
> *Nurse participant 17*

Some nurses also reported a need for additional training in tympanometry and interpretation to provide ongoing screening at their surgery. Others reported concerns about not seeing sufficient children with glue ear to maintain their skill level.

> *I think if it's just basic tympanometry I'd be happy to do it. I think – on having said that – I think if I am doing it, I would like more training just so – because – you know – it's nice to tell people – have information and knowledge so that you know what you're telling them.*
>
> *Nurse participant 18*

Referral expectations

Having their concerns listened to by GPs was very important to parents. Some parents reported that their concerns were not always recognised, and this resulted in repeat consultation and requests for onward referral.

> *Quite often they expected to be referred . . . and, you know, often – not often, but a few times I would get – the GP to come in just for – for reassurance, to say this is the glue ear season and even if we referred now, then maybe we would wait for a few months to see if things cleared naturally.*
>
> *Nurse participant 2*

Engaging with monitoring and treatment

This theme is defined as the importance of engaging parents and children in the screening process, AM and autoinflation for OME in primary care.

Interactions between nurses and families

Nurse–parent–child interactions were important for engaging families with primary care screening and compliance with the nasal balloon. Nurses reported good relationships with the children and their families. Parents often reported nurses to be more accessible than their GP colleagues, and having more time to spend with the children.

A good demonstration by the nurse, together with involvement of the parents, ensured that the children engaged with autoinflation treatment.

> *I demonstrated and they would then have a go and they – obviously weren't particularly good at it so I said to the mum – oh – you have a go and if you can do it, that helps the child.*
>
> *Nurse participant 12*

Some children had initial problems inflating the balloon, but in most cases this was overcome quickly and almost all children mastered the technique within a few days.

> *A couple were just scared of the idea but once they were shown whatever – and even if they just blew it a bit, then we sort of said – oh that's brilliant. And then, of course, the next time you saw them, they'd been blowing it up to the size of an orange.*
>
> *Nurse participant 2*

The 'fun' element of the balloon was often reported as appealing to the children. This led to the children taking ownership of the treatment:

> *Well, the girls thought that was great fun, anything to do with balloons isn't it? They think it's great and the gross factor of blowing it up with your nose is a real hit with the little ones. They love it.*
>
> *Parent participant 5*

Compliance with autoinflation

Overall, compliance was good during the first month of treatment. Making the balloon part of the daily routine made it easier for families to adhere to the treatment regimen.

> *in the morning whatever we were doing, and then at bedtime, so it was just like cleaning your teeth, just brought it in as an extra thing to do as part of the routine.*
>
> *Parent participant 6*

Positive feedback with reward sticker charts and the 'fun' element of the nasal balloon helped towards adherence over a longer period.

> *I think the sticker chart – I mean that definitely – having their reward book and different bits and pieces, I think that was – yes – that was a bit of an incentive.*
>
> *Nurse participant 2*

By contrast, some parents reported the novelty wearing off and others became frustrated with their children for not continuing. Unlike a medication that needs to be swallowed, autoinflation requires the child's active participation and this could become a battleground for parents.

> *So we staggered along for a few weeks with her not really trying to do it and, yes, it was just becoming such a pain, really. It was so painful to try and get her to do it and my husband was very supportive and we were both trying to encourage her to do it and I tried everything.*
>
> *Parent participant 4*

Discussion

This nested qualitative study of primary care monitoring and autoinflation in children with OME highlights the potential for an improved and more proactive role for general practice in the earlier diagnosis and treatment of this common childhood condition.

Primary care management of glue ear

The first point of contact for parents who have concerns about their child's hearing is usually primary care; they often present with a range of concerns, background knowledge and expectations for the diagnosis and treatment of their child.

This study found that parents wanted to take action once they had received a diagnosis, and that waiting was not always acceptable to them. For them, action involved taking medications, surgery and autoinflation. In a study of AOM, parents with more knowledge and who felt included in medical decisions were more likely to accept watchful waiting, rather than immediate antibiotic treatment.[97] OME naturally shows some improvement in ≈50% of cases by 3 months, rising to 75% at 6 months depending on the health-care system and on tympanometric criteria used to define improvement,[30] so there is a valid case for waiting for natural resolution of OME to occur.

Access to good-quality information about the natural history, causes and risk factors, treatments and preventative measures may help parents to rationalise and make informed choices concerning the management of their child. Written information has been found to increase the trust in verbal medical advice and reduce the need to obtain additional information elsewhere.[98] Ensuring that information fulfils the needs of parents with children with OME may be of particular importance considering the evidence of a link between parent views and treatment-seeking behaviours.[99]

Nurses were competent and skilled in managing children with glue ear, providing information, diagnosis with otoscopy and tympanometry, monitoring during the initial 3-month period and managing their treatment with the nasal balloon. It has been argued that nurses do not have the skills or sufficient training to conduct tympanometry.[100] Most of this research has been conducted in secondary care, where tympanometry diagnosis has been compared directly with the best relative standard of myringotomy ('relative' because of substantial dry tap rates at myringotomy), giving a direct measure of specificity and sensitivity for detecting middle ear effusions.[101] In the secondary care environment, multiple rigorous measures of bilateral OME causing persistent hearing loss are required as part of the AM process prior to undertaking grommet surgery, a requirement of the NICE guidelines.[1] However, in primary care, it is more useful to improve the early diagnosis of glue ear, to be able to start treatment as problems arise rather than allowing the condition to develop to the point of needing an operation. The latter may be considered a more substantial intervention from the child and family perspective.

Interactions

Building alliances in health care is an important part of helping towards a positive outcome and an important element of self-care.[102] Therapeutic alliances, most commonly reported in psychotherapy, may be a useful way of looking at the relationships between the nurse, parent and child in the case of primary care monitoring of OME. The model of therapeutic alliance was developed from the early work of Bordin,[103] who described the relationship between the practitioner and patient in terms of personal and collaborative relationships, and the effect they have on patient outcomes.[104] Our study has shown that the personal relationships between nurses and families can affect parental confidence in the information and diagnosis they receive and, consequently, the care that their child is receiving in primary care. The nasal balloon demonstration draws on the task element of this collaborative relationship and the combination of the nurse demonstration, parental involvement and engaging the child in the process has been shown to be important in children mastering the technique of autoinflation. The triadic relationship between the nurse, parent and child has been explored in asthma review consultations, which found that the individual dyadic relationships between nurse–parent, nurse–child and parent–child needed to be taken into account where there could be potential areas of conflict and lack of co-operation.[105] In this study, nurses reported focusing their attention on the relationship with the child, and seeing that co-operation at an early stage would be important for compliance with the procedure.

Acceptability and compliance

There have been both trial and anecdotal concerns from ENT centres that children may not be able to reliably perform autoinflation and that adherence to the treatment regimen may be a problem, especially in younger children. This study reported that the nasal balloon was perceived as an acceptable technique. School children mastered the technique relatively quickly, and adherence over the period of a month was achievable for most parents.

Acceptability to families of the nasal balloon has been reported in three previous secondary care studies, in which the technique was described as 'acceptable'[58] and 'fun' or 'amusing' for the children.[56,61] This is consistent with the findings of this study, where parents described the nasal balloon as a natural and holistic treatment, found it acceptable as a treatment and children are reported to enjoy the novelty of the technique. However, some children reported initial anxieties around the use of the balloon that were overcome with parental support and encouragement.

Previous studies have reported that young children had difficulty in mastering the technique of autoinflation, especially at the beginning. One study, which evaluated the use of Otovent after flying, found that just 53% of children aged 2–6 years could inflate the balloon.[106] However, the authors suggested that the children could have learnt the technique from their parents if they had commenced training 1–2 days before the flight. Accounts from this qualitative study suggest that most children became proficient at autoinflation after some practice. Stretching the balloon beforehand by oral inflation (by child or parent) helped with initial inflation, together with the encouragement and support of the parents.

Parents reported that the key to remembering to use the nasal balloon was to make it part of the child's everyday routine, such as after cleaning their teeth or using their asthma inhaler. Routines and rituals are important organisers of family life.[107] Children naturally adopt routines such as eating meals, daily homework and bedtime routines. It has been theorised that adopting good routines can improve the likelihood of compliance with certain medical treatments[108] and minimise the burden to families.[109] Adopting autoinflation as part of a routine may be very important for the longer-term use of the nasal balloon up to 3 months.

Strengths and limitations of the qualitative study

This research is the first to provide pragmatic, experiential data about use of autoinflation from a primary care setting, and includes both nurse and parent participant perspectives. It covers screening, AM and the use of the nasal balloon from the views of both the parents and primary care nurses. Using more than one data source to obtain different perspectives allows triangulation of the findings to check and establish study validity.[110]

The study has also given insight into day-to-day, real-life experiences of children using the nasal balloon, which has not hitherto been formally captured in previous studies of autoinflation. This study information should help identify the common enablers and barriers to the wider implementation of autoinflation in a community setting.

It was not possible to recruit parents of children who withdrew or dropped out of the AIRS. Their experiences of screening, monitoring and treatment may well have differed to the study group, such that possible problems associated with AM and compliance with the autoinflation treatment may be missing. It might have also been useful to gather views and opinions from the participating GPs, especially regarding primary care-led services. Also missing were the direct voices of the children themselves. Including children in research can enhance the scope and findings of a study;[111] however, in this instance the children were individually considered too young to be able to separately contribute to this study (predominantly 4–6 years).

Implications for clinical practice

The findings suggest that primary care professionals are eminently capable of engaging families early on in the process of AM with autoinflation and can provide good-quality information while drawing in parents and children in co-operative management decisions. Good demonstration/training with the autoinflation method, together with positive reinforcement by the health professional, will enhance child co-operation and improve overall adherence to the treatment schedule. Parents reported autoinflation to be acceptable to their children and compliance was improved by making the treatment part of the daily routine. However, the sample of parents had a somewhat higher than average educational level and were from areas of low social deprivation. Therefore, it would be of much interest to explore the potential barriers to autoinflation in lower socioeconomic groups where OME may have disadvantageous impacts.

Parents viewed practice nurses as accessible, local and able to provide continuity of care for OME. However, it remains uncertain as to exactly how a nurse-led service would work in the wider context of general practice, and this requires further research.

Chapter 7 Discussion

Principal findings

We report the results of the first pragmatic trial of the clinical effectiveness and cost-effectiveness of autoinflation that is generalisable to primary care, that is, to the majority of children attending practices with typical symptom clusters and impaired QoL linked to OME. It is the largest of the relatively few RCTs to date reported from either primary care or the community for any type of medical/non-surgical intervention,[1,45] and the largest trial on autoinflation to date performed in any health setting.[35] There are currently no proven non-surgical interventions for glue ear, which often leads to inappropriate treatment with antibiotics and other ineffective remedies.[1] A NNT of 9 for autoinflation shows it to be a reasonably effective method for clearing middle ear effusions when using stringent tympanometric criteria of resolution. The method also significantly and importantly reduces the level of ear concerns and symptoms that include reported hearing loss, earache, difficulty concentrating and consequent impaired QoL for both child and family over a 3-month period.

We found autoinflation to be a simple, low-cost procedure that appears to be moderately easy to teach to appropriate-age selected children (attending school) in a primary care setting, with good reported compliance. Blowing up a balloon through the nose is an acceptable relatively non-invasive option with potential to add benefit to guideline recommended 'watch and wait' or surveillance processes, which are commonly performed in primary care and the community. It is thus an intervention with considerable potential to be used at scale in the NHS.

Research in context of other studies

The most recent Cochrane review of autoinflation,[35] which highlighted the need for a large primary care trial, included three hospital studies of the same low-cost device trialled here. Adding our data to the meta-analysis more than doubles the available sample size of studies using similar outcomes with an estimated aggregate effect size (RR of improvement) of 1.61 (95% CI 1.26 to 2.06; I^2 heterogeneity 0.0%).

Tympanometry findings can be misleading when comparing studies, particularly because different studies can class type C2 as resolved or improved. As we regard C2 as poorly predictive of effusion status, we have not considered such cases as sufficiently resolved and hence our resolution rates will be lower than in studies that present C2 as improved/resolved.

Effect on quality of life

Although clearance of effusions is a necessary and important physiological outcome, it is known that there is only poor correlation between tympanometry and audiometry (hearing level),[2] and between audiometry and QoL.[19,21] For the child and parent, the most important issues are the expressed concerns about the consequential impacts caused by the OME.[75] Significant impacts of OME have been found in general practice settings to rival the impacts seen in UK secondary care settings.[21,30] These impacts include recurrent physical illness, hearing, speech and developmental impairments, and total effects on child and parent QoL. Taken from this perspective, the improved difference in the global OMQ-14 score of –0.42 points between arms (representing a moderate effect size) is both important and encouraging.

Feasibility and compliance

Children found autoinflation fun to do. In addition, the training method of demonstration by the nurse, then parent and then the child, was associated with good acceptability and engagement. With practice, nearly all the children mastered the technique: 89% of parents reported good compliance in their child's use of the balloon at 1 month, and 80% at 3 months. Making the treatment part of daily routine could enhance compliance, especially over a longer period.

Adverse events and safety

Parent-reported adverse events were similar between groups. There were, however, more mild URTIs and mild to moderate otalgia, which usually settled quickly, in the treated arm. This contrasts with fewer URTIs found in two hospital studies.[55,56] A single case of mastoiditis in the treatment arm was reported to the DMEC, who conducted a full, independent review. They concluded that the case of mastoiditis could not be attributed to autoinflation and that it was safe to continue the trial (see *Appendix 7*).

Strengths

A key strength is that the study population is representative of typical cases of OME seen in primary care, that is, in most cases parents had recently expressed relevant concerns that suggested OME, and OME had been clinically confirmed at the point of initiating treatment. The findings are therefore likely to be generalisable to a majority of affected children. We think that the observed aggregate effects, in terms of both consistent direction and the magnitude of effect sizes, across a range of repeated tympanometric and clinical outcomes, strengthen the plausibility and reliability of our findings.

The trial methodology was rigorous in other ways; for example, a power calculation was performed and a large sample achieved within the allocated time frame, web randomisation was used, and the executor and generator of randomisation were kept entirely separate. The execution and generation of randomisation was done by a company using computer-generated randomised sequences and stratified according to an analysis plan. The trial was analysed on an ITT basis (and PP), with objective evidence of OME (both at trial entry and as an outcome), good treatment compliance $\geq 80\%$, and a very modest loss to follow-up of $\approx 10\%$. Patient and public involvement contributed to various aspects of the trial. Feedback about the practicalities and training of the treatment method from parents whose children participated in the pilot was incorporated into the main study. A lay member of the Trial Steering Committee, also a parent of children with glue ear, contributed to study recruitment strategies and had input into the qualitative evaluation.

All practice nurses had training in trial protocol and methods used, for example otoscopy and tympanometry. Two authors and one external audiologist, who were all blind to treatment allocation, independently reviewed the outcome assessments at 1 and 3 months. Nurses showed a substantial level of agreement with expert interpretation of tympanometry as a relative standard ($\kappa > 0.7$), which improved as the study progressed. Completion rates of trial forms (case report forms) were very high and multiple imputation methods were used for all missing data both at 1 and 3 months. A CONSORT diagram is provided (see *Figure 5*), with separate baseline tables for both the screened and entered populations.

Limitations

The main limitation of the study was that using a nasal balloon is a method that cannot be blinded and Hawthorne effects are possible.[112] However, the lack of blinding is unlikely to affect the primary tympanometric outcomes and, even if symptom and mapped QoL scores are affected by performance bias, the effects observed are still likely to be commensurate with those found in routine clinical practice. The HE analysis suggests that trial behaviour was very similar in both arms, and the PP analysis was not different from the ITT analysis in terms of effects. The study population included children who were deemed likely to be able to reliably perform autoinflation ($\geq$ 4.5 years), whereas the usual presentation pattern to primary care and ENT clinics in the UK is from approximately 3.5 to 8 years. This does not mean that younger children cannot perform the technique – some children as young as 3 years have been able to use the device in secondary care,[28,29] and even younger than 3 years when a novel counter-pressure method is used.[65]

Clinical implications

At the time of writing there are no known effective non-surgical treatments that have been proven to be satisfactory to apply in primary care and the community for children with the tenacious cluster of symptoms and impacts that characterise OME.[2,7,12,23] The study findings of a treatment, a device, that actually works for OME in primary care has potential when judiciously applied to fill the 'management gap' in current practice that exists between either doing nothing effective or referring the worst cases for surgery (often after incurring long delays). Temporising strategies, an attempt to let nature take its course, are often seen as unreasonable delay(s) by parents. Some strategies, such as prescribing antibiotics, are a misplaced attempt to fill the therapeutic vacuum, because they are inappropriate, ineffective and harmful, and contribute a major threat to public health in the form of antibiotic resistance.

Although finding the method effective over 3 months, because fluid in the ear does not fully resolve in about half of all children who use autoinflation in the short term, and with the known tendency to recur, continued vigilance with consideration of surgical referral must remain a central consideration in evidence-based management of children presenting with OME.

In this study we have used relatively rigorous measures of diagnosis, impact and outcome, but there is no reason to suppose that GPs' and practices' own routine criteria for identifying cases of OME are generally inadequate or insufficient, given the time and demand pressures on the NHS. Like many areas of current health care, however, there is always scope for better definition of the problem needing fixing. The characteristic symptoms and concerns of OME are presented in *Box 1* and the OMQ-14 that was used in the study (see *Appendix 5*). They are distinct from acutely presenting otitis media with fever and pain, and more problematic to child and family than those of simple self-limiting viral illnesses. The more frequently the child attends with relevant ear symptoms and concerns, the clearer that the case becomes for treatment. A secondary analysis found three symptoms/concerns: any ear concern in the previous 3 months; mis-hearing what is said; and needs the television turning up. These three symptoms together produce 70% of the area under the ROC curve, which is a reasonably good indication for management purposes where tympanometry is not available. However, it must be accepted that tympanometry is only a relative and not a gold standard. Treatment criteria clearly depend on the case being considered, and secondary care criteria for intervention, somewhat embedded in current clinical culture (perhaps because grommets are the only known effective treatment), cannot be used as a basis for any treatment applicable to an earlier case stage in a primary care context, where the therapeutic aim is timely and proportionate remediation.

Although autoinflation is generally acceptable with brief instruction, it may not be suitable for all, particularly children aged under 4 years, and does require regular ongoing commitment to treatment. The method is deemed to have scope to be used in the majority of routine symptomatic cases, and thus is capable of improving satisfaction with management and outcomes in primary care. It should be more widely used.

Chapter 8 Conclusion

Implications for practice

This clinical trial is the first of its type in a primary care setting. It is one of the largest trials reported for interventions for OME from any setting. Considering the current evidence base for non-surgical interventions systematically, one is led to the conclusion that there is no prior justification for any cost-effective treatment for OME, at the point in the NHS where the majority of children are initially identified and treated. Furthermore, medical treatments that are presently applied as part of temporising management are not only ineffective but also harmful. The latter is particularly the case for antibiotics.

Our findings reveal that autoinflation using the balloon method is feasible in primary care. A NNT of 9 at both 1 and 3 months was found for improved clearance of middle ear effusions, beyond what can be expected from natural resolution effects alone (standard care). The symptom diaries (hearing loss, earache, etc.) showed significant and encouraging improvements by 3 months, a recommended waiting time, as did the mapped ear-related QoL measure (PROM). The effect size for effusion clearance is comparable to that achieved when smaller secondary care studies are combined in Cochrane and makes the case for wide use of autoinflation more robust.

Our sample characteristics are considered generalisable to primary care populations, of which they are reasonably representative in terms of both the baseline severity of the effusions and the prior number of typical symptoms and concerns expressed. There are relatively few exclusion criteria and the sample, although heterogeneous, has demonstrated important clinical effects. Baseline severity markers and method of recruitment were shown in the statistical models to have no effect on the primary treatment outcomes, which is an important clinical finding. The main limitation in terms of generalisability is the age of the children recruited in to the study because of age-related limitations with the method. Surgical studies have demonstrated effectiveness when recruiting children as young as 3 years,[55,56] but compliance is likely to be poorer in such age groups.

In terms of capacity to change clinical practice, we have demonstrated that this method can augment the current natural resolution process in a beneficial, inexpensive, safe and timely fashion for the majority of children with symptomatic OME. It should therefore be an attractive initial option when one considers the unsatisfactory nature of present 'temporising' or available management options, which include usually either offering advice only or giving a 'known' ineffective and harmful treatment such as antibiotics or a decongestant, or referring the child prematurely for further evaluation for surgery.

Clinically, assuming the status quo of children identified in primary care across the UK with a working diagnosis of OME, the majority will be eligible for empirical management – the modus vivendi of primary care practitioners. Thus, although there are inevitable limits to what one can conclude from a large open pragmatic trial, the sum of the new evidence appears sufficiently strong to justify far wider use of this intervention than is currently the case.

Recommendations for future research

- The findings from this study should be reviewed in wider terms, for example relevance to current practice by multiprofessional groups to aid positioning and prudent application. There is potential to be considered in updates to the Cochrane meta-analysis of autoinflation and review of future NICE guidelines for OME.
- Further pragmatic research should be undertaken to evaluate the relative benefits of:
  - usual care in practices plus or minus autoinflation using HE and standardised outcomes
  - improved diagnostic care for recurrent otitis media/OME using trial-developed symptom predictors of effusions/impact measures or by selective use of tympanometry in primary care practices
  - shared care with other agencies.

  Such research work should aim to offer more effective integrated approaches for children recognised with OME symptoms and concerns in primary care.
- To improve the management of OME in primary care by the development of tools that encourages and promotes self-efficacy. Development of a web-based support intervention could provide evidence-based patient information, practical support for use of nasal balloon autoinflation to enhance uptake and compliance.
- To evaluate selective screening and monitoring of at-risk children in primary care, using age, attendance records, near patient hearing tests and/or short-form QoL questionnaires. This has potential to address Tudor Hart's inverse care law,[33] but needs to be shown to be cost-effective.
- Treatment failures are an important group for further research in primary and secondary care settings. Randomised trials would be helpful to determine the probable effectiveness of autoinflation as a re-treatment, treatment before surgery in hospital and also effectiveness in prevention of second operations for grommets.
- The youngest children are an important group for further research. To evaluate different autoinflation methods that evaluate comparative effectiveness and feasibility in relation to the age-related competence of the child. New methods using counter pressure may be promising for the very youngest children.
- There is potential scope for basic science technical development of the study device in relation to drug delivery to the Eustachian tubes.
- To evaluate the clinical effectiveness of oral steroids, which may be considered appropriate for young age groups or for treatment failures (of autoinflation), or for children seen in hospital prior to surgery. [Current research in progress includes a randomised trial funded by the NIHR HTA programme that addresses relevant issues (HTA reference number 11/01/26).]
- To update the epidemiology of otitis media with use of databases, for example Clinical Practice Research Database, with better differentiation of OME from recurrent AOM.

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Contributions of authors

Ian Williamson (Associate Professor, University of Southampton and chief investigator) conceived and designed the study, led protocol development and the funding application. Also contributed to the analysis and interpretation, and led the drafting of all chapters of the report.

Jane Vennik (Trial Manager, University of Southampton) provided day-to-day management, co-ordinated recruitment and contributed to the data collection, analysis and interpretation. Also led the design, data collection, analysis and reporting of the qualitative study. Contributed to drafting of the all chapters of the report.

Anthony Harnden (Professor of General Practice, University of Oxford) contributed to protocol development and funding application, and contributed to the drafting of all chapters.

Merryn Voysey (Senior Statistician, Oxford PCVC-CTU) led the statistical analysis of the study and contributed to drafting *Chapters 3* and *4*.

Rafael Perera (Associate Professor, University of Oxford) contributed to the protocol statistics section and advised on drafts.

Maria Breen, Brendan Bradley and **Sadie Kelly** (Data Officer, Senior Data Specialist and Head of Trials, Oxford PCVC-CTU, respectively) provided CTU oversight for both the pilot and the main study, and contributed to the main trial design. Also supervised and managed the randomisation process, data collection, cleaning and validation, and commented on drafts of all chapters of the report.

Guiqing Yao (Associate Professor of Health Economists, University of Southampton) co-led the HE analysis and drafting of *Chapter 5*.

James Raftery (Professor of Health Economists, University of Southampton) co-led the HE analysis and drafting of *Chapter 5*.

David Mant (Emeritus Professor of General Practice, University of Oxford) contributed to protocol development and funding application, contributed to the drafting of all chapters.

Paul Little (Professor of Primary Care Research, University of Southampton) contributed to protocol development and funding application, contributed to the drafting of all chapters.

Contributors to protocol and pilot study

Dr Sarah Benge (Trials Unit Manager, Oxford PCVC-CTU) contributed to protocol development for the funding application.

Ms Michelle Caneppele (Trial Co-ordinator, PCVC-CTU) provided day-to-day management of the pilot study, including interpretation and reporting.

David Turner (Health Economist, University of Southampton) developed the HE plan.

Jing Jin (Statistician, Oxford PCVC-CTU) contributed to trial design and developed the statistical analysis plan.

Members of the Trial Steering Committee

Mr James Ramsden (chairperson), Professor Chris Frost, Dr Anthony Harnden, Dr Tim Whelan, Dr Ian Williamson (chief investigator) and Dr Rachel MacDonald (lay member).

Members of the Data Monitoring and Ethics Committee

Professor Kerry Hood (chairperson) and Mr Emeka Okpala.

Data sharing statement

All available data can be obtained from the corresponding author.

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Appendix 1 National Research Ethics Service approval and amendments to the study

NHS

National Research Ethics Service
SOUTHAMPTON & SOUTH WEST HAMPSHIRE RESEARCH ETHICS COMMITTEE (B)
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
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SO16 4RJ

Tel: [redacted]
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RK/STA/hph

10 August 2009
(amended 17 August 2009)

RECEIVED
19 AUG 2009

Dr I G Williamson
Senior Lecturer
University of Southampton
Primary Medical Care
Aldermoor Close
Southampton
Hampshire
SO16 5ST

Dear Dr Williamson

Study Title: **An open randomised study of autoinflation in 4-11 year old school children with otitis media with effusion (OME) in primary care.**
REC reference number: **09/H0504/75**
Protocol number: **2**
EudraCT number:

Thank you for your letter of 06 August 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Alternate Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
GP Information for Pilot Study	1	06 November 2008
Draft Letter for Invitation to Screening: Parent Letter 2	1	06 November 2008
Appendix 2: Participant flow through Study	1	
Appendix 1: Flow Chart	1	17 March 2009
Participant Consent Form: Parent	1	06 November 2008
GP/Consultant Information Sheets	1	06 November 2008
Covering Letter		29 April 2009
Application		29 April 2009
GP Interest Fax Back Form	1	06 November 2008
Patient Flow	1	06 November 2008
Questionnaire: Initial Appointment Form	1	06 November 2008
Questionnaire: HUI- 3 Months	1	06 November 2008
Questionnaire: HUI - Baseline	1	06 November 2008
Questionnaire: Parent: 3 Month Measures (OM8-30)	1	06 November 2008
Questionnaire: Parent: Baseline Measures (OM8-30)	1	06 November 2008
Compliance Reward Chart	1	06 November 2008
Diary 2	1	06 November 2008
Diary 1	1	06 November 2008
Questionnaire: 1 Month Measures Form	1	06 November 2008
Questionnaire: 2-4 day post baseline compliance check + follow-up appointment if necessary	1	06 November 2008
Questionnaire: Baseline About you and your child	1	06 November 2008
Questionnaire: Baseline Measures Form	1	06 November 2008
Questionnaire: First Screening Form	1	06 November 2008
Questionnaire: Health Resource Use at 6 Months	1	06 November 2008
Questionnaire: 3 Month Measures Form	1	06 November 2008
Compensation Arrangements		23 April 2009
Letter from Sponsor		23 April 2009
Investigator CV		20 April 2009
Response to Request for Further Information		23 July 2009
Participant Consent Form: Assent	2	25 June 2009
Participant Information Sheet: 4-5 year olds	2	25 June 2009
Protocol	2	03 July 2009

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Draft Letter for Invitation to Screen: Parent Letter 1	3	05 August 2009
Response to Request for Further Information		06 August 2009
Participant Information Sheet: Patient (6-11 years old)	3	05 August 2009
Participant Information Sheet: Parent	3	05 August 2009

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email [redacted]

09/H0504/75 **Please quote this number on all correspondence**

Yours sincerely

Professor R King
Alternate Vice-Chair

Email: [redacted]

Enclosures: "After ethical review – guidance for researchers" SL- AR2 for other studies

Copy to: Dr Martina Prude
University of Southampton

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Ethics committee approval and amendments to the protocol

Amendment number	Amendment date	Summary of changes
Ethics committee approval	10 August 2009	
Amendment 1 (minor)	27 August 2009	• Minor changes to consent form •
Amendment 2	29 Sept 2010	• Protocol changes: clarification of randomization procedures •
Amendment 3	29 March 2010	• Addition of a pilot study survey for nurses to gain feedback for the main trial.. •
Amendment 4	7 April 2011	• New exclusion criteria (recurrent nosebleeds) • Web-based randomization • Improved version of parent questionnaire • Minor changes to protocol, invitation letters, information sheets and questionnaires
Amendment 5	6 October 2011	• Changes to CRFs and questionnaires following successful pilot • Additional questionnaires and CRFs (Heath Resources and Costs to Parents) • Minor changes to protocol to add clarity
Amendment 6	31 May 2012	• Minor changes to the invitation letter to enable use of DocMail (not used) • Parent Information card for the TADAST web hearing test • Poster for Waiting Room
Amendment 7	12 July 2012	• Agreement for over-recruitment to a maximum of 350 children • Approval for re-invitation of children from previous season
Amendment 8	14 August 2012	• Detailed methods of qualitative evaluation- parents and nurses
Amendment 9	9 May 2013	• 12 month notes review
Amendment 10	17 March 2014	• Detailed methods of qualitative evaluation – GPs

Appendix 2 Recruitment materials

Practice Headed Paper

DRAFT LETTER FOR INVITATION TO SCREENING (Parent letter 1)

To the parents/guardians of.....

Our practice is taking part in a research project looking at "glue-ear" in children – its medical name is "Otitis Media with Effusion". The research is funded by the NIHR Health Technology Assessment Programme and managed by the University of Southampton. We have enclosed an information sheet about the study and also one for your child.

"Glue-ear" is a very common condition in the early school years, and it affects about 4 out of 5 children before their 10th birthday.It is also particularly common over the winter months. It is a type of catarrh, sticky mucus or "glue" behind the eardrum, which can cause the child to lose some hearing and lead to a variety of different problems. Most children affected by this condition will recover on their own over 3 months, however a small percentage may need further medical treatment.

Your child has been invited because they are 4-6 years old and we have shown in other studies that even seemingly healthy children in this age range quite commonly get glue ear in the winter and spring terms (about 1 in 4 children on average and sometimes higher).

Please use this checklist of any ear concerns for the last 3 months and if your child has a tick against one or more of these then glue ear is a possibility and at very least worth excluding, so we would like to invite your child into the practice to have their ears screened (and if found positive - treated).

SYMPTOM CHECKLIST		
A prolonged or bad cold, cough or chesty infection	☐ Yes	☐ No
An earache	☐ Yes	☐ No
Appears to mishear what is said	☐ Yes	☐ No
Hearing loss has been suspected by anyone	☐ Yes	☐ No
Says 'eh what?' or 'pardon' a lot	☐ Yes	☐ No
Needs the television turned up	☐ Yes	☐ No
May be irritable or withdrawn	☐ Yes	☐ No
Appears to be lip reading	☐ Yes	☐ No
Not doing so well at school as you or the teacher think *e.g.* with reading	☐ Yes	☐ No
Has noises in the ear or is dizzy	☐ Yes	☐ No
Snores, blocked nose or poor sleep	☐ Yes	☐ No
Speech seems behind other children's	☐ Yes	☐ No
Any suspected ear problem	☐ Yes	☐ No

AIRS Parent letter for 4-6 year olds Version 4, 23-02-11

If your child has <u>not</u> had any of these symptoms or concerns in the last 3 months then there is no benefit of coming in for a screening just now and there is no need to read any further, but we would ask that you kindly return the completed reply slip below.

If your child has however had one or more of these symptoms or concerns then it is good to confirm if they actually have glue ear as the cause using a simple quick painless test, (using a soft ear probe like a headphone). The study will then compare a treatment technique called autoinflation and your doctor's usual management against your doctor's usual management only. Autoinflation involves your child blowing up a special balloon using their nose rather than their mouth (see picture). Your child will have a 50:50 chance of receiving autoinflation straight away to take for one to three months, with all study children receiving usual clinical care for their glue ear.

If a study child in the group not receiving autoinflation still has glue ear after a test three months later (the more persistent or troublesome cases) then they will be offered autoinflation to use if they want. If your child does take part in the study we would just ask you to keep a simple diary of their symptoms with their help. Following the initial appointment the practice research nurse will make two appointments to see you and your child over three months to monitor their ears. She will ask you to complete a questionnaire on these visits.

You are under no obligation to take part in the study. If you decide not to take part in this study it will not affect the care that you or your children would receive from the practice in any way. You have the right to withdraw from the study at any time and if you do so it will not affect the care that you or your child(ren) receive from the practice.

If you have any questions or concerns please do not hesitate to contact the research nurse ..... at the practice on the telephone number above.

If you are interested in attending an initial appointment, with your child, for a fuller explanation and discussion of the study and a confirmation (diagnostic) screening by the research nurse, please complete the attached reply slip and return it in the stamped addressed envelope. It would be helpful if you would kindly return this reply slip even if you do not wish to attend an appointment.

Please read the enclosed Patient Information Sheet and please give your child the one we've enclosed especially for them.

Yours sincerely

Dr Doctor

AIRS Parent letter for 4-6 year olds Version 4, 23-02-11

Study ID number: | | | | | | | |

PLEASE TICK YES TO EITHER A or B
then return to the practice in stamped addressed envelope provided

A **My child has one or more symptoms in the checklist** **YES** ☐

I agree / I do not agree for my child and I to be seen by the nurse for a fuller explanation of the study and to confirm if they have glue ear using an accurate diagnostic test

(the tympanometry screening for glue ear, will only be done if you agree on the day)

Your Name: .....

Child's Name: .....

Tel: .....

OR

B **My child does not have any of the symptoms in the checklist and therefore does not need a screening test** **YES** ☐

AIRS Parent letter for 4-6 year olds Version 4, 23-02-11

Practice Headed Paper

DRAFT LETTER FOR INVITATION TO SCREENING (Parent letter 2)

To the parents/guardians of……..

Our practice is taking part in a research project looking at "glue-ear" in children – its medical name is "Otitis Media with Effusion". The research is funded by the NIHR Health Technology Assessment Programme and managed by the University of Southampton. We have enclosed an information sheet about the study and also one for your child.

"Glue-ear" is a very common condition affecting about 4 out of 5 children before their 10th birthday, and is particularly common over the winter months. It is a type of catarrh, or "glue" behind the eardrum, which can cause the child to lose some hearing and lead to a variety of different problems. Most children affected by this condition will recover on their own, however a small percentage may need further medical referral and treatment.

If your child has glue ear in one or both ears they could join in with our research. The study will compare a treatment technique called autoinflation and your doctor's usual management against your doctor's usual management only. Autoinflation involves your child blowing up a special balloon using their nose rather than their mouth (see picture).

Your child will have a 50:50 chance of receiving autoinflation straight away to take for one to three months, with all study children receiving usual clinical care for their glue ear.

If any study child in the group not receiving autoinflation still has glue ear after a test three months later (the more persistent or troublesome cases) then they will be offered autoinflation to use if they want. If your child does take part in the study we would ask you to just keep a simple diary of their symptoms with their help. Following the initial appointment the practice research nurse will make two appointments to see you and your child over three months to monitor their ears. She will ask you to complete a questionnaire on these visits.

Your child has been invited because your practice has noted from their records that they have had one or more ear infections or ear related problems over the last year and he/she may therefore have developed glue ear.

You are under no obligation to take part in the study. If you decide not to take part in this study it will not affect the care that you or your child(ren) receive from the practice in any way. You have the right to withdraw from the study at any time and if you do so it will not affect the care that you or your child(ren) receive from the practice.

If you have any questions or concerns please do not hesitate to contact the research nurse ..... at the practice on the telephone number above.

If you are interested in attending an appointment, with your child, for a fuller explanation and discussion of the study and an initial confirmation (diagnostic) screening by the research nurse, please complete the attached reply slip and kindly return it in the stamped addressed envelope. It would be helpful if you would return this reply slip even if you do not wish to attend an appointment.

Please read the enclosed Patient Information Sheet and please give your child the one we've enclosed especially for them.

Yours sincerely

Dr Doctor

Study ID number: | | | | | | | |

Please circle and return to the practice in stamped addressed envelope provided.

I agree / I do not agree for my child and I to be seen by the nurse for a fuller explanation of the study and to have an initial screening for glue ear, if I agree on the day

Your Name: .....

Child's Name: .....

Tel: .....

Appendix 3 Parent and child information sheets

UNIVERSITY OF Southampton
School of Medicine

Autoinflation Randomised Study in school age children (4-11 years) with glue ear (AIRS).

Parent Information Sheet

Invitation

Your child is being invited to help with a research study looking at "glue ear" or "Otitis Media with Effusion" (which is its medical name) and whether a technique called autoinflation is a good treatment for it. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to discuss it with your GP or the research nurse at the practice. You can also obtain further information about the study by contacting us at the address given at the end of this information sheet.

What is the purpose of the study?

"Glue ear" is a very common condition in children and is particularly common over the winter months. It is a type of catarrh or "glue" behind the eardrum, which can cause the child to lose some hearing and lead to a variety of different problems. Many children affected by this condition will recover on their own, however some children also have recurrent or persistent catarrh in their ears and may need further medical treatment and possibly referral. This study aims to see whether auto-inflation can help improve the health and quality of life of such children.

Why has my child been chosen?

Your practice has noted from their records that, 1) Your child is at an age where glue ear is quite common and is just about to start or has recently started school this year, or 2) They have already had one or more ear infections or ear related problems over the last year that may be associated with glue ear noted in your child's health records. They are therefore inviting you to an appointment with the practice research nurse for a test that can detect if your child currently has any "glue" behind the eardrum. This is a simple painless five minute test.
We have shown in other studies that even seemingly healthy children aged 4-6 years old often get glue ear in the winter and spring terms (about 1 in 4 children on average per term and sometimes higher).

Does my child have to take part?

No. It is completely up to you to decide whether your child takes part or not. If you do decide to take part you are still free to withdraw at any time and you do not have to give a reason. If you do decide not to take part or to withdraw your child from the study this will not affect the standard of care you or your child receive from the practice.

What will happen to my child if they take part in the study?

If you agree that your child can take part, then you and your child will be asked to come into the practice for an appointment with the research nurse to have an ear test. The ear test can accurately detect any "glue" behind the eardrum. If your child is found to have "glue" behind one or both of their ears then this will be deemed sufficient to confirm a degree of impaired hearing for them to be considered eligible to enter the study.

If you decide to let your child participate in the next part of the study, your child will be allocated at random to either the autoinflation method of treatment and usual care or they will receive usual care only from their GP (*e.g.* a decongestant, information or watchful waiting). Being allocated at random is like tossing a coin to decide

which group your child is in. We are doing this because we do not yet know if autoinflation is an effective treatment but several studies suggest it is.

Your child will continue with their initial assigned treatment (for one month after which they will come to see the research nurse again for another ear test. If your child's ear(s) are better they will not continue with any treatment, **however** if their ear (or at least one of their ears) is not better your child will be asked to continue treatment (autoinflation and usual care or just usual care) for a further two months. We ask all study children to come back and see the research nurse at the end of the treatment/usual care period for a final check to see if all is clear at three months. Study children that were not in the autoinflation group and still have glue ear after a test three months (the more persistent or troublesome cases) will be offered autoinflation at that point to use if they want. Study children that received autoinflation for three months and still have glue ear at the three month test will be asked to see their GP.

During the time your child is taking part in the study we will ask you to keep a simple diary, filled in once a week for convenience, about your child's symptoms and how they are. You will be asked to do this for the first month and the second two months (three months in total). At each visit we will ask you to complete some questionnaires about your child and their health. The practice nurse will also check your child's notes at six months after they entered the study, looking for ear related consultations over that time.

What will my child have to do?

Your child will have to have their ears tested at the beginning of the study. Your child may or may not be then suitable to go further into the study, this depends on whether or not they have glue ear in at least one ear, and whether you and your child are happy to be randomised into the study.

If your child is in the autoinflation treatment group you and your child will be shown how to use the balloon by the nurse. Your child will have to use this 3 times a day every day for one month in the first instance and then if not cured for a further two months.

All children will receive usual care and they will receive the standard treatment provided by your practice for your child's condition such as a decongestant, information, watchful waiting or referral. Your child will need to carry out whatever usual care instructions given by your GP/practice for three months.

All children in the study will be asked to have three ear tests, one will be at the beginning of the study, the second will be one month later and the third will be a total of three months from starting the study.

Some children will be asked to repeat the screening test straight after using the balloon to see if we can predict who will get better fastest.

What is autoinflation?

This is a technique in which a child blows up a special balloon using their nose rather than their mouth. The purpose is to open the Eustachian tube (the tube that connects the middle ear to the throat) and allow pressure in the middle ear to return to normal. Continued use of autoinflation over several weeks has been shown to help some children with glue ear get better faster. Autoinflation is a 'low-tech' way of helping some children, with no known harms. It can be made into a game, but it needs adult supervision and it may require quite a little practice at first so it is important to persevere.

What are the benefits of my child taking part?

Your child's usual care will not be affected in any way. Benefits include accurate monitoring of progress and offering autoinflation, a new treatment suggested to help by the National Institute for Health and Clinical Excellence (NICE). The small studies done so far look promising, suggesting auto-inflation may indeed be an effective treatment, particularly when children are school aged and prepared and able to use the treatment regularly. This approach may avoid more serious glue ear developing and subsequent referral and grommets in some children. The research is being done to clarify if and how effective this new treatment is. We do know it is very safe indeed from all the studies done so far.

What are the possible risks/side effects of my child taking part?

There have been no reported side effects of using this balloon so far. It does produce a pressure change in the nose comparable to swimming under water at a depth of about 2 feet. The idea that this blows germs into the ear from the back of the nose seems unlikely, especially since the previous British small study showed that ear infections were in fact more common when the balloon was not used than when it was. Most people accept that "blowing the nose" is good hygiene for both children and adults. We will however monitor any potential side effects such as an increase in respiratory infections.
Using the nose to blow up a balloon can be uncomfortable, especially the first few times this is done. The nurse will advise how to stretch the balloon to minimise any discomfort

Medical Indemnity Arrangements

If your child is harmed by taking part in this research project then they are covered by the University of Southampton's Indemnity Insurance. If you are harmed as a result of general clinical management, for example due to someone's negligence then you are covered by the GP's own indemnity insurance. Regardless of this, if you do wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms will be available to you.

What happens when the research study stops?

The autoinflation treatment is available over the counter, so when the study has ended you and your child will be able to carry on using it should you wish to purchase it or alternatively your GP could prescribe it if they thought it was suitable for your child's condition before the results of this study were published.

Will my child taking part in this study be kept confidential?

Yes. A study number will be used instead of your child's name and address. This means that the data collected will be kept anonymous. All information will be treated in accordance with the Data Protection Act.

What will happen to the results of the research study?

It is anticipated that the results of the study will be published a year after the conclusion of the research. No child will be identified by name in any publication.

Who is organising the funding of the research?

The University of Southampton is the sponsor of this study and the NIHR Health Technology Assessment Programme is the funder. Unfortunately we are unable to reimburse you for your travel expenses.

Contact for further information

The Study Manager, *name to be inserted*, Primary Care and Population Sciences Division, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST. Telephone *number to be inserted*

What if I have any other concerns?

If you have any problems, concerns or other questions about this study, you should contact The Study Manager, *name to be inserted* at the above address or discuss them with the research nurse or GP at your practice.

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect you and your child's safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the Southampton and South West Hampshire Research Ethics Committee.

THANK YOU FOR READING THIS DOCUMENT AND FOR ANY HELP YOU DECIDE TO GIVE

IF YOU DO CHOOSE TO LET YOUR CHILD TAKE PART IN THE STUDY PLEASE KEEP THIS INFORMATION SHEET AND YOU WILL ALSO GET A COPY OF YOUR SIGNED CONSENT FORM

YOU AND YOUR CHILD ARE FREE TO WITHDRAW FROM THE STUDY AT ANYTIME

UNIVERSITY OF Southampton
School of Medicine

Autoinflation Randomised Study in school age children (4-11 years) with glue ear (AIRS).

Patient Information Sheet for 6-11 year olds

What is research? Why is this study being done?

Research is an important way we try to find out the answers to questions using science - a way of discovering things. We want to see if blowing up a balloon (like in the picture) treats poorly ears better than what is usually used.

What autoinflation means is blowing up a balloon using your nose just like in this picture!

Why have I been asked to take part?

It is possible you may have sticky ears which are something a lot of children get. Doctors and adults call it glue ear. This means that hearing quiet noises like whispers or what people are saying can be hard sometimes, especially when there is a lot of noise being made by other people. Your doctor is helping us with a study to find out better ways of treating sticky-glue ear.

Who has checked the study is ok and safe to do?

Before any research is allowed to happen, it has to be checked by a group of people called a Research Ethics Committee. They make sure that the research is fair. Your study has been checked by the *to be inserted* Research Ethics Committee.

Do I have to take part?

No you don't have to take part in this study and even if you do take part you can leave at any time, it's up to you.

What will happen to me if I decide to take part in the study?

If you want to join in here's what will happen. First you will have your ears tested by the nurse, then if you have sticky ear you may be asked to use either the balloon three times a day, or we may just keep an eye on you for a while to check it goes away. You and your parents will keep a diary of how you feel. You will see the nurse 3 times and she is able to see you after school or in the holidays so you don't need to miss any school.

Primary Medical Care
University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST, United Kingdom

Tel: [redacted] Fax: [redacted]

Will blowing up the balloon with my nose upset me?

No, it will just feel a little bit like blowing your nose when you blow up the balloon. For the first few times blowing up the balloon can be uncomfortable. No children have been hurt doing this and you can stop blowing whenever you want. Once the balloon has been blown up a few times it gets much easier to do just like when you blow up balloons with your mouth.

Might anything else about the study upset me?

We don't think there will be anything about joining in that will upset you, but if you do become upset by something please let your parents know and they can phone the nurse or you can tell the nurse when you see her again.

Will joining in help me?

We cannot promise the study will definitely help you. The information we get should help treat children with sticky ears in better ways in the future. You will get a chance to have a go with the balloons if you have got sticky ears, either straight away or later. So far it looks good that these balloons do help make it go away.

What happens when the study stops?

At the end of the study you will have helped us to see if the balloon is a good way of helping children with sticky-glue ear. It may take us a while to work this out but during that time if you wanted to still use the balloon you could ask your doctor to give it to you on a prescription or your grown ups could buy it from a chemist shop. So if you find it helped you, you can keep using it for longer.

What if something goes wrong ?

We do not think that anything will go wrong during the study but if it did we (your doctor, nurse and the University of Southampton) would make sure no harm comes to you and we would make sure everything was put right.

What if a better medicine or treatment comes along?

If this happens it will not matter that you are helping us with this study, you will get the treatment that is best for you.

What if I don't want to do the study anymore?

If at any time you don't want to do the study anymore, just tell your parents, doctor or nurse. They will not be cross with you. Your doctor will help you decide which medicine or treatment is best to use afterwards.

If you have any questions ask the nurse and they will try to answer them.

*This information sheet is to be given to the patient if aged between **6 and 11 years of age** in addition to the parents receiving the more detailed patient information sheet.*

Version 3, 05/08/2009

UNIVERSITY OF Southampton
School of Medicine

Autoinflation Randomised Study in school age children (4-11 years) with glue ear (AIRS).

Patient Information Sheet for 4 and 5 year olds

To be shown/read to the child by their parent/guardian

It can sometimes get a little sticky inside children's ears. This may make it hard for some children to hear whispers and people speaking - especially when there is a lot of noise being made all around.

Your doctor is helping us to find out ways of getting children with sticky ears better as quick as we can

If you like you can help us by joining in.

If you want to join in here's what will happen.

You can see what will happen in the picture.

You will have your ears tested by the nurse. It will not hurt, but you will hear a buzzing noise and might feel a tiny "pop"

Afterwards you may then be asked to blow up a special balloon three times a day using your nose to see if it makes the ear better.

You can see this in the picture.

Blowing up the balloon like this can be a little tricky at first. But it gets much easier to do after you have practised it a few times. It soon gets more comfortable and can be fun to do - seeing how big you can get the balloon!

Your mummy or daddy will ask you how you are feeling and how your ears are while you get them better again. If you have any questions about helping us please ask the nurse and they will answer them for you.

YOU CAN STOP WHENEVER YOU LIKE

Version 2, 25/06/2009

Primary Medical Care
University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST, United Kingdom
Tel: [redacted] Fax: [redacted]

Appendix 4 Consent forms

Medicine

UNIVERSITY OF Southampton

Centre:

Study number: 09/H0504/75

Study ID number: | | | | | | | |

CONSENT FORM

Autoinflation Randomised Study in school age children (4-11 years) with glue ear (AIRS).

(Version 3, 23-02-11)

Name of Chief Investigator: Dr Ian Williamson

Please initial box

1. I confirm that I have had the study explained to me by the research nurse, and had the chance to read the parent information sheet (Version 4, dated 23-02-11) and either the 4-5 year old (Version 2, dated 25-06-2009) or the 6-11 year old patient information sheet (version 3, dated 05-08-2009) and ask questions that have been answered satisfactorily. ☐
2. I understand that all my child's details will be kept confidential and their name will not appear on any reports or documents. ☐
3. I understand that taking part in the study will involve further trips for me and my child to the surgery. ☐
4. I am happy for my child to have their ears checked immediately after using the balloon with an extra tympanogram. ☐
5. I understand that if my child participates in the randomised part of the study and is randomised to use the autoinflation treatment, I will need to make sure they perform the treatment as instructed, and that the total length of treatment is up to three months. ☐
6. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from an NHS Trust where it is relevant to my child taking part in this research. I give permission for these people to have access to my child's records. ☐
7. I understand that our participation is voluntary and that we are free to withdraw at any stage without giving reasons and without my or my children's medical care or legal rights being affected. ☐
8. I agree to my GP being informed of my child's participation in the study. ☐
9. I agree to my child taking part in this study. ☐

Name of Parent	Signature	Date
Name of research nurse	Signature	Date

White copy: GP practice, Yellow copy: Southampton University, Green copy: Patient

Primary Medical Care
University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST, United Kingdom

Tel: [redacted] Fax: [redacted]

Medicine

UNIVERSITY OF Southampton

Centre:

Study number: 09/H0504/75

Study ID number: | | | | | | | |

To be completed by the child and their

ASSENT FORM

Autoinflation Randomised Study in school age children (4-11 years) with glue ear (AIRS).
(Version 2, 25/06/2009)

Have you read (or had read to you) about this study?	Yes/No
Has somebody else explained this study to you?	Yes/No
Do you understand what this study is about?	Yes/No
Have you asked all the questions you want?	Yes/No
Have you had your questions answered in a way you understand?	Yes/No
Do you understand it's OK to stop taking part at any time?	Yes/No
Are you happy to take part?	Yes/No

If any answers are 'no' or you don't want to take part, you don't need to

If you do want to take part, you can write your name below

Your name ..... Date .....

The nurse who explained this study to you needs to sign too:

Name of research nurse ..... Date .....

Thank you for your help

White copy: GP practice, Yellow copy: Southampton University, Green copy: Patient

Primary Medical Care
University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST, United Kingdom

Tel: [redacted] Fax: [redacted]

Appendix 5 The 14-point questionnaire on the impact of OME (OMQ-14)

OFFICE USE ONLY: study/clinic identifiers.....

OMQ-14: Quality of Life in children's ear problems

Questionnaire on impact of ear problems in children 3-9 years*

How parent/caregiver should complete this questionnaire

Some children are more affected than others, and in differing ways. Help can best be given, and improvement best assessed, when this impact is measured in a standard way that bridges these differences. The following 14 questions cover some of the most important ways in which ear problems affect children's quality of life. For some questions an interpretation may be involved, not just an observation, so an "unsure" response is permitted. But please try to avoid this, by choosing the response that best describes just how affected your child has been over the last 3 months, and placing a tick-mark (√). On finishing, please check that you have answered all questions. The answers will be kept confidential to the clinic or research team.

All questions refer to the period of the last 3 months.

		FOR OFFICE USE ONLY
1. Over the last three months, taking everything into account, how has your child's health has been ?		
Very good	☐	
Good	☐	
Only fair, or poor	☐	
2. How many times has he/she had trouble with his/her ears ?		
Not at all	☐	
Once	☐	
2-3 times	☐	
4 or more times	☐	
3. How many ear infections has he/she had ? ***(i.e. severe pain in his/her ear, possibly with a temperature, smelly discharge in ear canal, or hole in eardrum)***		
0	☐	
1	☐	
2-3	☐	
4 or more	☐	

*. Exceptionally, the questionnaire can be used after a child becomes 9 years old (see User Manual)

All questions refer to the last 3 months.

		FOR OFFICE USE ONLY
4. How many times has he/she had an earache ?		
0	☐	
1	☐	
2-3	☐	
4 or more	☐	
5. How would you describe your child's hearing ?		
Normal	☐	
Slightly below normal	☐	
Poor	☐	
Very poor	☐	
Not sure	☐	
6. Has he/she mis-heard words when not looking at you ?		
No	☐	
Rarely	☐	
Often	☐	
Always	☐	
Not sure	☐	
7. Has he/she had difficulty hearing when with a <u>group</u> of people ? ***(ie not one-to-one)***		
No	☐	
Rarely	☐	
Often	☐	
Always	☐	
Not sure	☐	

All questions refer to the last 3 months.

		FOR OFFICE USE ONLY
8. How long can he/she concentrate on a game or a task <u>you have given him/her to do</u> ?		
Up to 2 minutes	☐	
Up to 5 minutes	☐	
5-10 minutes	☐	
10-15 minutes	☐	
More than 15 minutes	☐	
9. How often does he/she seek your attention unnecessarily ? ***(e.g. in an unusually dependent way, asking for help for a task he/she can do alone, demanding to be carried, demanding you play with them, following you around)***		
Less than once a month	☐	
Once a month	☐	
Once a week	☐	
Once a day	☐	
Two or more times per day	☐	
10. How often is he/she unhappy for no apparent reason ?		
Less than once a month	☐	
Once a month	☐	
Once a week	☐	
Once or more per day	☐	
11. Has he/she mispronounced the beginnings or ends of words ?		
No	☐	
Rarely	☐	
Often	☐	
Always	☐	
12. Has his/her speech been behind (less developed than) that of children of similar age ?		
No	☐	
A little	☐	
Moderately or a lot	☐	
Not sure	☐	

	FOR OFFICE USE ONLY
13. Have you often felt tired ?	
Yes ☐	
No ☐	
14. Has your child needed more attention than other children ?	
Yes ☐	
No ☐	

Responding person providing information

A. Would you describe your educational qualifications as:				Score 1
Left school before age 15 years	☐	Usual school exams for 15-16	☐	
Usual school exams for 17-18	☐	Further qualifications, but not university degree	☐	Score 2
University degree	☐	Not applicable	☐	

B. Are you:				Score 3
Child's mother	☐	Child's father	☐	
☐ Other (please specify).....				
Your own age.....| Age of child:.....				

C. If any impacts from the ear problems of your child which you think important have <u>not</u> been covered above, please mention up to 4 here:

1. .....

2 .....

3 .....

4 .....

DOI: 10.3310/hta19720

AIRS: Initial Appointment Form

Study ID Number:

Date of Appointment: d d m m y y y y

Gender: ☐ Female ☐ Male

Age: ☐☐ years ☐☐ months

Patient's first name: …… Patient's surname: ……

Postcode: …… Telephone: ……

Address: ……

Date of Birth: ……

Q1. Was this child recruited from:

☐ 4-6 year old list (go to Q2) ☐ 7-11 year old list (go to Q3) ☐ GP/Nurse/HV referral (go to Q3)

Q2 Please ask which symptom(s) their child has had in the last 3 months:

		Yes	No			Yes	No
(a)	A cold, cough or chesty infection	☐	☐	**(h)**	Appears to be lip reading	☐	☐
(b)	An earache	☐	☐	**(i)**	Not doing as well at school as you or the teacher reasonably think	☐	☐
(c)	Often mishears what is said	☐	☐	**(j)**	Has noises in the ear or is dizzy	☐	☐
(d)	Hearing loss is suspected by anyone	☐	☐	**(k)**	Snores, blocked nose or poor sleep	☐	☐
(e)	Says 'eh what?' or 'pardon' a lot	☐	☐	**(l)**	Speech seems behind other children's	☐	☐
(f)	Needs the television turned up	☐	☐	**(m)**	Any suspected ear problem	☐	☐
(g)	May be irritable or withdrawn	☐	☐				

Q3. Please answer the following questions from your OBSERVATION REGISTER:-

a) Was this child recruited from: ☐ computer records **OR** ☐ referral

b) If he/she was recruited from their records please state:

How many episodes of OME have they had in the last 12 months ……

How many episodes of OM have they had in the last 12 months ……

Have they had 1 or more entries in their notes over the last 12 months for

i) hearing loss **Yes / No** if yes, how many ……
ii) snoring **Yes / No** if yes, how many ……
iii) behaviour concerns **Yes / No** if yes, how many ……
iv) speech concerns **Yes / No** if yes, how many ……
v) educational concerns **Yes / No** if yes, how many ……

Q4. INCLUSION AND EXCLUSION CRITERIA (go through with parent/guardian)

a) Is your child too young to be at school or older than 11 years? Yes ☐ No ☐

b) Does your child have grommets in place? Yes ☐ No ☐

c) Is your child already listed for an operation to have grommets put in? Yes ☐ No ☐

d) Has your child had a recent nose bleed (within the last 3 weeks) or more than one episode of nose bleeding over the past 6 months? Yes ☐ No ☐

e) Does your child have an allergy to latex? Yes ☐ No ☐

f) Has a clinician made you aware that your child may need early referral for glue ear? (e.g. children with Down's, cleft palate, Kartagener's, Primary Ciliary Dyskinesia, immunodeficiency states etc.) Yes ☐ No ☐

g) Does the nurse believe your child will be **unable** to comply with the technique of autoinflation? Yes ☐ No ☐

If the answer to **ALL** these questions is **NO** the child is **ELIGIBLE** for screening please go to Question 5

If at least one answer is **YES** the child is **NOT ELIGIBLE** for screening, please give the parent an explanation as to why – refer to you study manual. Please go to Question 6

Q5. CONSENT (parent informed about trial)

☐ Consent obtained

☐ Consent form taken away, to be posted back

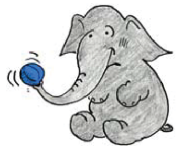
If parent refuses to consent, ask them if they are happy to give their reasons, if they are please state them here……

……

☐ Child (parent) given a copy of their signed consent form and patient information sheet(s)

Q6. Nurse's signature: _____ **Date:** _____

AIRS: First Screening



Study ID Number: | | | | | | | | |

Date of Appointment: | d | d | m | m | y | y | y | y |

Q1. OTOSCOPY FINDINGS *please circle*:

	mostly clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry	**mostly wax**	RIGHT	LEFT
	perforation	RIGHT	LEFT
exclude child from study ←	**grommet**	RIGHT	LEFT

Q2. TYMPANOMETRY

Please circle one option for each ear and fill in the pressure reading

RIGHT EAR	LEFT EAR
A C1 B C2	A C1 B C2
Pressure = ……daPa	Pressure = ……daPa

Please attach print out here

Large amounts of wax (>95% obscured) and a **low** compliance (<0.2ml)	☐ Yes	☐ No	**if yes, exclude**
Perforation, **flat line** and **high volume** (>1.5ml)	☐ Yes	☐ No	**if yes, exclude**

Q3. ELIGIBILITY

a) If ***NOT ELIGIBLE***, please tick box indicating that the child has been excluded from study and explanation has been given to the parent/guardian and child as to why. If child is **NOT ELIGIBLE** please go to Question 5 ☐

b) If ***ELIGIBLE***, continue to Question 4

Q4. PARENT INFORMED ABOUT NEXT PART OF STUDY ☐ Yes ☐ No

If parent does not wish to continue please give their reason(s) for refusal

……

……

Q5. OPTIONAL

Appointment made with yourself or GP as part of *standard clinical care** ☐ Yes ☐ No

If yes, please specify the date(s) ……..

This is your standard management (i.e. watchful waiting, antibiotics, nose drops, referral or other treatment) for glue ear which you would do or advise to the patient if the trial were not taking place.

Q6. Nurse's signature: _____ **Date:** _____

AIRS First Screening Form Version 3, 10-08-11

AIRS: Baseline – About You and Your Child

Study ID Number: | | | | | | | | |

Date of Appointment: | d | d | m | m | y | y | y | y |

TO BE COMPLETED BY THE PARENT

Nurse – put green copy back in folder once completed

1. Does your child have any of these?

Asthma	☐ Yes	☐ No
Hay fever	☐ Yes	☐ No
Eczema	☐ Yes	☐ No

2. Has your child had antibiotics for an ear infection or ear problem in the last month?

☐ Yes ☐ No

3. What is the highest grade of school you have completed?

	You	Partner
School to 16, no qualifications	☐	☐
School to 16, GCSE's/O'Levels	☐	☐
Sixth form school or college, A' levels, ND	☐	☐
Highers, Scotvec or NVQ	☐	☐
University degree	☐	☐
Professional or postgraduate degree	☐	☐

4. Which of the following best describes your current marital status?

Married or living with partner	Single	Separated or divorced	Widowed
☐	☐	☐	☐

5. Which of the following best describes YOUR CHILD'S racial background

White	Oriental	Afro-Caribbean	Bangladeshi / Indian	Mixed race	Other group
☐	☐	☐	☐	☐	☐

If mixed race or other group, please specify …….

6. Is English the first language spoken at home?

☐ Yes ☐ No

If NO, which language is used? .....

7. What is your annual gross family income (before any tax deductions and including Benefits)?

less than £10k	£10k - £20k	£21k - £30k	£31k - £40k	£41k - £50k	over £50k
☐	☐	☐	☐	☐	☐

AIRS Baseline about you and your child (reformatted) version 2, 23-02-11

AIRS: 1 Month Measures Form

Study ID Number: | | | | | | | | |

Date of Appointment: | d | d | m | m | y | y | y | y |

4 week diary collected	Yes ☐	No ☐	
Reward Chart collected	Yes ☐	No ☐	N/A ☐

IF THE CHILD WAS RANDOMISED TO STANDARD CARE PLEASE START WITH QUESTION 2

Q1. AUTOINFLATION ADHERENCE AND USE

a) Did your child perform the autoinflation?

☐ not at all ☐ some of the time ☐ most of the time ☐ all of the time

b) How many times per day did your child use it?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ More than 3

c) How many blows in each nostril did your child do?

☐ 0 ☐ 1 ☐ More than 1

d) How easy do you think your child found the autoinflation to do?

Extremely easy	Very easy	Moderately easy	Fairly easy	Not very easy	Not easy at all
☐	☐	☐	☐	☐	☐

e) Could you describe any discomfort your child experienced whilst doing the autoinflation

……

……

Was it at the start of the study? ☐ Yes ☐ No

Was it throughout the study? ☐ Yes ☐ No

Q2. CHECK REFERRAL STATUS

Has your child been referred to an ENT surgeon	☐ Yes	☐ No
If yes, has the surgeon recommended surgery	☐ Yes	☐ No
If yes, do you have an appointment yet date ……	☐ Yes	☐ No

Q3.CHECK ADVERSE EVENTS / SIDE EFFECTS

Increase in respiratory infections	☐ Yes	☐ No
Occurrence of nose bleeds	☐ Yes	☐ No

If child and/or parents are concerned about their side effects or it is severe they should be referred to the GP

If any Adverse Events are reported please complete an Adverse Event Form with parent present

AIRS 1 month measures form (reformatted) Version 3, 10-08-11

AIRS: 1 Month Measures Form

Study ID Number: | | | | | | | | | **PAGE 2 of 2**

Q4. OTOSCOPY *please circle for each ear*:

	mostly clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry	**mostly wax**	RIGHT	LEFT
	perforation	RIGHT	LEFT
child continues with study ←	**grommet**	RIGHT	LEFT

Q5. TYMPANOMETRY

a) Please circle one option for each ear and fill in the pressure reading

RIGHT EAR	LEFT EAR
A C1 B C2	A C1 B C2
Pressure = ……daPa	Pressure = ……daPa

Please attach print out here

b) Large amounts of wax (>95% obscured) and a **low** compliance <0.2ml) ☐ Yes ☐ No

c) Perforation, **flat line** and **high volume** (>1.5ml) ☐ Yes ☐ No

Q6. COMMENT: ☐ cooperative ☐ non-cooperative

Q7. AUTOINFLATION GROUP - IF CHILD HAD AT LEAST ONE B TYMPANOGRAM AT THIS VISIT

Has the child been given more Otovent supplies? ☐ Yes ☐ No

If No, why not? ……..

Q8. STANDARD CARE GROUP ONLY

Has your child used any autoinflation devices between baseline and 1 month?

☐ Yes ☐ No

Q9. OPTIONAL

Appointment made with yourself or GP as part of *standard clinical care** ☐ yes ☐ no

If yes, please specify the date(s) ……..

This is your standard management (i.e. further watchful waiting, antibiotics, nose drops, referral or other treatment) for glue ear which you would do or advise to the patient if the trial were not taking place.

Q10. Nurse's signature: _____ **Date:** _____

AIRS 1 month measures form (reformatted) Version 3, 10-08-11

AIRS: 3 Month Measures Form

Study ID Number: | | | | | | | | |

Date of Appointment: | d | d | m | m | y | y | y | y |

8 week diary collected	Yes ☐	No ☐	
Reward Chart collected	Yes ☐	No ☐	N/A ☐

Q1. Please tick one of the following:

☐ Child randomised to Autoinflation and had **at least one B tympanogram at 1 Month** (go to Q2)

☐ Child randomised to Autoinflation and had **no B tympanograms at 1 Month** (go to Q3)

☐ Child randomised to Standard Care (go to Q3)

Q2. AUTOINFLATION ADHERENCE

a) Did your child perform the autoinflation

☐ not at all ☐ some of the time ☐ most of the time ☐ all of the time

b) How many times per day did your child use it?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ More than 3

c) How many blows in each nostril did your child do?

☐ 0 ☐ 1 ☐ More than 1

d) Could you describe any discomfort your child experienced whilst doing the autoinflation

.....

.....

Q3. CHECK REFERRAL STATUS

Has your child been referred to an ENT surgeon	☐ Yes	☐ No
If yes, has the surgeon recommended surgery	☐ Yes	☐ No
If yes, do you have an appointment yet	☐ Yes	☐ No

When .....

Q4. CHECK ADVERSE EVENTS/SIDE EFFECTS

Increase in respiratory infections	☐ Yes	☐ No
Occurrence of nose bleeds	☐ Yes	☐ No

If child and/or parents are concerned about their side effects or it is severe they should be referred to the GP

If any Adverse Events are reported please complete an Adverse Event Form with parent present

AIRS 3 month measures form (reformatted) Version 3, 10-08-11

AIRS: 3 Month Measures Form

Study ID Number: | | | | | | | | |

Q5. OTOSCOPY *please circle one for each ear*:

	mostly clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry	**mostly wax**	RIGHT	LEFT
	perforation	RIGHT	LEFT
child continues with study ←	**grommet**	RIGHT	LEFT

Q6. TYMPANOMETRY

a) Please circle one option for each ear and fill in the pressure reading

RIGHT EAR	LEFT EAR
A C1 B C2	A C1 B C2
Pressure = ……daPA	Pressure = ……daPA

Please attach print out here

b) Large amounts of wax (>95% obscured) and a **low** compliance (<0.2ml) ☐ Yes ☐ No

c) Perforation, **flat line** and **high volume** (>1.5ml) ☐ Yes ☐ No

Q7. COMMENT: ☐ cooperative ☐ non-cooperative

Q8. Has your child used any autoinflation devices between 1 and 3 months (for autoinflation group this refers to devices other than the Otovent given to you for study purposes)?

☐ Yes ☐ No

Q9. OPTIONAL

Appointment made with yourself or GP as part of *standard clinical care** ☐ yes ☐ no

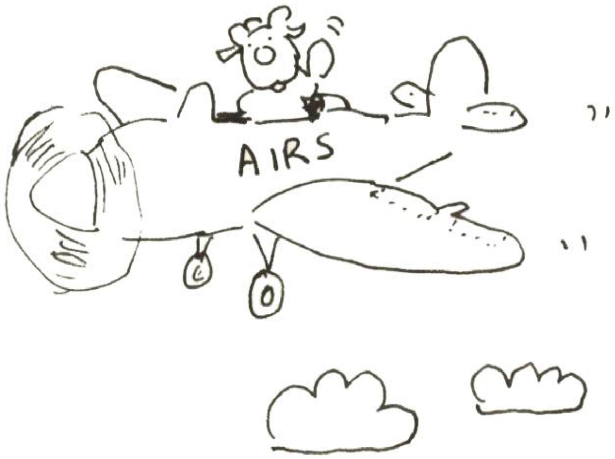
If yes, please specify the date(s) ……..

This is your standard management (i.e. further watchful waiting, antibiotics, nose drops, referral or other treatment) for glue ear which you would do or advise to the patient if the trial were not taking place.

Q10. Nurse's signature: _____ **Date:** _____

AIRS 3 month measures form Version 3, 10-08-11

AIRS



Diary 1

For YOU

This is your diary and you and your grown ups need to fill it in at the end of each week – they will ask you to remember how you have felt over the week and then they will write it down so think hard because we can't wait to hear how you've been feeling.

For the GROWN-UPS of the AUTO-INFLATION GROUP

Please remember that your child needs to blow the balloon up (once in each nostril, three times throughout the day) at whatever time suits you best but please do it at the same time each day

Version 1, 06/11/2008

WEEK 1 (EXAMPLE)

1. How many days has your child had earache (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
	✓						

2. How many days has your child had any hearing loss (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
		✓					

3. How many days has your child had a problem concentrating (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
		✓					

4. How many days has your child had off school / playgroup (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
			✓				

5. How many days has your child received pain relief (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
				✓			

6. How many **nights** has your child had disturbed sleep (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
			✓				

Thinking only of this week:- tick whether or not your child had the symptoms in the table below and for the ones they did have use the following ratings to rate how bad each one got at its worst in the week

0 = not present at all 1 = very little problem 2 = slight problem 3= moderately bad 4 = bad 5 = very bad 6 = as bad as it could be

Has you child.....	Yes	No	how bad at its worst
been clumsy / off balance	✓		**4**
been unwell / had a temperature		✓	
had a runny nose	✓		**3**
had a blocked nose / been snoring		✓	
had any nosebleeds		✓	

WEEK 1

1. How many days has your child had earache (please put a cross in the relevant box)

0	1	2	3	4	5	6	7

2. How many days has your child had any hearing loss (please put a cross in the relevant box)

0	1	2	3	4	5	6	7

3. How many days has your child had a problem concentrating (please put a cross in the relevant box)

0	1	2	3	4	5	6	7

4. How many days has your child had off school / playgroup (please put a cross in the relevant box)

0	1	2	3	4	5	6	7

5. How many days has your child received pain relief (please put a cross in the relevant box)

0	1	2	3	4	5	6	7

6. How many **nights** has your child had disturbed sleep (please put a cross in the relevant box)

0	1	2	3	4	5	6	7

Thinking only of this week:- tick whether or not your child had the symptoms in the table below and for the ones they did have use the following ratings to rate how bad each one got at its worst in the week

0 = not present at all 1 = very little problem 2 = slight problem 3= moderately bad 4 = bad 5 = very bad 6 = as bad as it could be

Has you child.....	Yes	No	how bad at its worst
been clumsy / off balance			
been unwell / had a temperature			
had a runny nose			
had a blocked nose / been snoring			
had any nosebleeds			

WEEK 2

1. How many days has your child had earache (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

2. How many days has your child had any hearing loss (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

3. How many days has your child had a problem concentrating (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

4. How many days has your child had off school / playgroup (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

5. How many days has your child received pain relief (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

6. How many **nights** has your child had disturbed sleep (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

Thinking only of this week:- tick whether or not your child had the symptoms in the table below and for the ones they did have use the following ratings to rate how bad each one got at its worst in the week

0 = not present at all | 1 = very little problem | 2 = slight problem | 3= moderately bad | 4 = bad | 5 = very bad | 6 = as bad as it could be

Has you child.....	Yes	No	how bad at its worst
been clumsy / off balance	☐	☐	
been unwell / had a temperature	☐	☐	
had a runny nose	☐	☐	
had a blocked nose / been snoring	☐	☐	
had any nosebleeds	☐	☐	

WEEK 3

1. How many days has your child had earache (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

2. How many days has your child had any hearing loss (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

3. How many days has your child had a problem concentrating (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

4. How many days has your child had off school / playgroup (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

5. How many days has your child received pain relief (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

6. How many **nights** has your child had disturbed sleep (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

Thinking only of this week:- tick whether or not your child had the symptoms in the table below and for the ones they did have use the following ratings to rate how bad each one got at its worst in the week

0 = not present at all 1 = very little problem 2 = slight problem 3= moderately bad 4 = bad 5 = very bad 6 = as bad as it could be

Has you child.....	Yes	No	how bad at its worst
been clumsy / off balance	☐	☐	
been unwell / had a temperature	☐	☐	
had a runny nose	☐	☐	
had a blocked nose / been snoring	☐	☐	
had any nosebleeds	☐	☐	

WEEK 4

1. How many days has your child had earache (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

2. How many days has your child had any hearing loss (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

3. How many days has your child had a problem concentrating (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

4. How many days has your child had off school / playgroup (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

5. How many days has your child received pain relief (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

6. How many **nights** has your child had disturbed sleep (please put a cross in the relevant box)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

Thinking only of this week:- tick whether or not your child had the symptoms in the table below and for the ones they did have use the following ratings to rate how bad each one got at its worst in the week

0 = not present at all | 1 = very little problem | 2 = slight problem | 3= moderately bad | 4 = bad | 5 = very bad | 6 = as bad as it could be

Has you child.....	Yes	No	how bad at its worst
been clumsy / off balance			
been unwell / had a temperature			
had a runny nose			
had a blocked nose / been snoring			
had any nosebleeds			

You are a star – well done you finished your first diary.

AIRS: Costs to parents 1

To be completed when taking BASELINE measures

Study ID number: | | | | | | | |

1. SELF MEDICATION USE FOR EAR PROBLEMS

Over the **last 3 months** have you self-treated your child (without coming to surgery) for an ear problem?

a) Using decongestant or antihistamine medicines/tablets? ☐ Yes ☐ No

If YES, how many occasions? ☐ 0-1 ☐ 1-2 ☐ 2-4 ☐ More than 4

b) Using a nose spray? ☐ Yes ☐ No

If YES, how many occasions? ☐ 0-1 ☐ 1-2 ☐ 2-4 ☐ More than 4

c) Using pain relieving medicine such as paracetamol, calpol, junior ibuprofen? ☐ Yes ☐ No

If YES, how many occasions? ☐ 0-1 ☐ 1-2 ☐ 2-4 ☐ More than 4

2. TIME OFF WORK

a) Have you had to take any time off paid work in the **last 3 months** because of your child's ear problems?

Yes ☐ No ☐

If yes, how many days have you needed to take off work in the **last 3 months** _____ days

b) Has your partner, or any other members of your family needed to take time off work because of your child's ear problems?

Yes ☐ No ☐

If yes, how many days have you needed to take off work in the **last 3 months** _____ days

3. OTHER OUT OF POCKET EXPENSES

During the **last 3 months** have you had any extra expenses because of your child's ear problems? Please only include costs that arose because of your child's ear problem.

Examples might include: additional child care costs or taxi fares and other travel expenses.

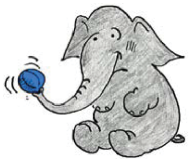
Yes ☐ No ☐

If yes, please say what this/these expense(s) were:-

Type of expense, please state	Approximate value in £s
EXAMPLE: taxi fare to collect from school early	*£15*
Expense 1……..….	
Expense 2……	
Expense 3……	
Expense 4……	

AIRS: Health Resource Use: +6 Months

To be done 6 MONTHS AFTER BASELINE by computer search



Study ID Number: | | | | | | | | |

Date Performed: | d | d | m | m | y | y | y | y |

All questions refer to the previous 6 month

Q1. ALL APPOINTMENTS

(excluding AIRS assessment appointments)

	Ear related	Non-ear related
List the dates of surgery appointments with GP		
List the dates of surgery appointments with practice nurse		
List the dates of surgery appointments with health visitor		
List the dates of home visits by GP		
List the dates of home visits by district nurse		
List the dates of home visits by health visitor		
List the dates of telephone consultations with GP		
List the dates of telephone consultations with practice nurse		
List the dates of out of hours consultations with GP		

Study ID Number: | | | | | | | |

Q2. TREATMENT COURSES FOR OM OR OME (EAR PROBLEMS)

a) Antibiotics:

date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..

b) Decongestants and antihistamines:

date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..

c) Analgesics:

date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..

Q3. PRESCRIBED MEDICATION FOR OTHER REASONS

date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..
date …….. name …….. dose …….. days ……..

Q4. ANY INVESTIGATIONS IN THEIR RECORDS

e.g. blood tests / x-rays,

please state, what …….. Date: …….. Number ……..
please state, what …….. Date: …….. Number ……..
please state, what …….. Date: …….. Number ……..

Q5. OUTPATIENT HOSPITAL REFERRALS

Date ……
main reason ……
to where?

☐ ENT ☐ audiology ☐ other
please state ……..

Date ……
main reason ……
to where?

☐ ENT ☐ audiology ☐ other
please state ……..

Please turn over

Study ID Number: | | | | | | | | **PAGE 3 of 3**

Date ……
main reason ……
to where?

☐ ENT ☐ audiology ☐ other
please state ……...

Date ……
main reason ……
to where?

☐ ENT ☐ audiology ☐ other
please state ……...

Q6. REFERRAL FOR SPEECH THERAPY

Date ……..
main reason ……
to where? ……

Date ……..
main reason ……
to where? ……

Q7. REFERRAL TO COMMUNITY HEALTHCARE PROFESSIONAL (e.g. community paediatrician)

Date ……..
main reason ……
to where? ……

Date ……..
main reason ……
to where? ……

Date ……..
main reason ……
to where? ……

Date ……..
main reason ……
to where? ……

Q8. HOSPITALISATION

Was the child admitted to hospital for:

a) grommets / t-tubes / ventilation tubes: Yes / No
b) adenoidectomy: planned Yes / No
done Yes / No
c) other reason Yes / No
if yes, please state ……

If Yes to a) or b) or c) please state:-

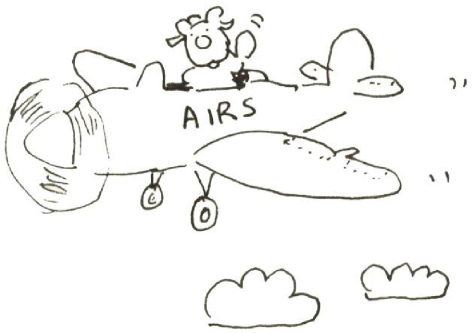
Name of hospital	Name of ward	Date of admission	Date of discharge
……	……..	……..	……..……
……	……..	……..	……..……

Q9. Nurse's signature: _____ **Date:** _____

AIRS Health resource use: +6 months Version 3, 10-08-11

HUI23P4E.15Q
Health Utilities Index Mark 2 and Mark 3 (HUI2/3)
15-item questionnaire for self administered, proxy-assessed
"Four week" Health Status Assessment

AIRS



1 Month

Study ID Number:

Date questionnaire completed:

d	d	m	m	y	y	y	y

Version 1., dated 20/05/2011

Permission for the use of this document was obtained from:

Health Utilities Inc. (HUInc)

88 Sydenham Street

Dundas ON, Canada L9H 2V3

Tel [redacted]

Fax [redacted]

http://www.healthutilities.com

Instructions for parents / guardians

This questionnaire contains a set of questions which ask about various aspects of your child's health. When answering these questions please think about your child's health and ability to do things on a day-to-day basis, **during the past 4 weeks**. To define the past 4 week period, please think about what the date was 4 weeks ago and recall the major events that your child has experienced during this period. Please focus your answers on your child's abilities, disabilities, and how they have felt during the past 4 weeks.

You may feel that some of these questions do not apply to your child, but it is important that we ask the same questions to everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

Please read each question and consider your answers carefully. For each question, please select **one** answer that **best describes** your child's level of ability or disability during the past 4 weeks. Please indicate the selected answer by circling the letter (a, b, c, ……) beside the answer.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your child's abilities and feelings.

1. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to see well enough to read ordinary newsprint?
   - **a.** Able to see well enough without glasses or contact lenses
   - **b.** Able to see well enough with glasses or contact lenses
   - **c.** Unable to see well enough even with glasses or contact lenses
   - **d.** Unable to see at all

2. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to see well enough to recognise a friend on the other side of the street?
   - **a.** Able to see well enough without glasses or contact lenses
   - **b.** Able to see well enough with glasses or contact lenses
   - **c.** Unable to see well enough even with glasses or contact lenses
   - **d.** Unable to see at all

3. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to hear what was said **in a group conversation with at least three other people**?
   - **a.** Able to hear what is said without a hearing aid
   - **b.** Able to hear what is said with a hearing aid
   - **c.** Unable to hear what is said even with a hearing aid
   - **d.** Unable to hear what is said, but does not wear a hearing aid
   - **e.** Unable to hear at all

4. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to hear what was said **in a conversation with one other person in a quiet room**?

   a. Able to hear what is said without a hearing aid
   b. Able to hear what is said with a hearing aid
   c. Unable to hear what is said even with a hearing aid
   d. Unable to hear what is said, but does not wear a hearing aid
   e. Unable to hear at all

5. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to be understood when speaking his/her own language with people who do not know them?

   a. Able to be understood completely
   b. Able to be understood partially
   c. Unable to be understood
   d. Unable to speak at all

6. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to be understood when speaking with people who know them well?

   a. Able to be understood completely
   b. Able to be understood partially
   c. Unable to be understood
   d. Unable to speak at all

Please turn over

7. Which **ONE** of the following best describes your child's feelings during the past 4 weeks?
   - **a.** Happy and interested in life
   - **b.** Somewhat happy
   - **c.** Somewhat unhappy
   - **d.** Very unhappy
   - **e.** So unhappy that life is not worthwhile

8. Which **ONE** of the following best describes the pain and discomfort your child has experienced during the past 4 weeks?
   - **a.** Free of pain and discomfort
   - **b.** Mild to moderate pain or discomfort that prevents no activities
   - **c.** Moderate pain or discomfort that prevents a few activities
   - **d.** Moderate to severe pain or discomfort that prevents some activities
   - **e.** Severe pain or discomfort that prevents most activities

9. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to walk?

Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

a. Able to walk around the neighbourhood without difficulty, and without walking equipment

b. Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person

c. Able to walk around the neighbourhood with walking equipment, but without the help of another person.

d. Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood

e. Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood.

f. Unable to walk at all

Please turn over

10. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to use his/her hands and fingers?

Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands and fingers.

a. Full use of two hands and ten fingers

b. Limitations in the use of hands or fingers, but does not require special tools or the help of another person

c. Limitations in the use of hands or fingers, independent with use of special tools (does not require the help of another person)

d. Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools)

e. Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools)

f. Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools)

11. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to remember things?
    - **a.** Able to remember most things
    - **b.** Somewhat forgetful
    - **c.** Very forgetful
    - **d.** Unable to remember anything at all

12. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to think and solve day to day problems?
    - **a.** Able to think clearly and solve day to day problems
    - **b.** Has a little difficulty when trying to think and solve day to day problems
    - **c.** Has some difficulty when trying to think and solve day to day problems
    - **d.** Has great difficulty when trying to think and solve day to day problems
    - **e.** Unable to think or solve day to day problems

Please turn over

13. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to perform basic activities?
    - **a.** Eats, bathes, dresses and uses the toilet normally
    - **b.** Eats, bathes, dresses and uses the toilet independently with difficulty
    - **c.** Requires mechanical equipment to eat, bathe, dress or use the toilet independently
    - **d.** Requires the help of another person to eat, bathe, dress or use the toilet

14. Which **ONE** of the following best describes your child's feelings during the past 4 weeks?
    - **a.** Generally happy and free from worry
    - **b.** Occasionally fretful, angry, irritable, anxious or depressed
    - **c.** Often fretful, angry, irritable, anxious or depressed
    - **d.** Almost always fretful, angry, irritable, anxious or depressed
    - **e.** Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help

15. Which **ONE** of the following best describes the pain or discomfort your child has experienced during the past 4 weeks?

- **a.** Free of pain and discomfort
- **b.** Occasional pain or discomfort. Discomfort relieved by non-prescription medication or self-control activity without disruption of normal activities
- **c.** Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional; disruption of normal activities
- **d.** Frequent pain or discomfort; frequent disruption of normal activities. Discomfort requires prescription medication for relief
- **e.** Severe pain or discomfort. Pain not relieved by medication and constantly disrupts normal activities

16. Overall how would you rate your child's health during the past 4 weeks?

- **a.** Excellent
- **b.** Very good
- **c.** Good
- **d.** Fair
- **e.** Poor

Please turn over

17. Who provided information used to answer the questions in this questionnaire? (please indicate all that apply)

a. Person recording the answers on the form

b. Child

c. Others. Please list the relationship between your child and each person who provided information:

1. ……

2. ……

3. ……

4. ……

18. Who recorded the answers on this questionnaire form?

a. Parent of the child

b. Other (please specify) ……

Many thanks for all your help

BASELINE MEASURES

Date of completion | d | d | m | m | y | y | y | y |

Study ID Number | | | | | | | | |

OMQ-14: Quality of Life in children's ear problems

Questionnaire on impact of ear problems in children 3-9 years*

How parent/caregiver should complete this questionnaire

Some children are more affected than others, and in differing ways. Help can best be given, and improvement best assessed, when this impact is measured in a standard way that bridges these differences. The following 14 questions cover some of the most important ways in which ear problems affect children's quality of life. For some questions an interpretation may be involved, not just an observation, so an "unsure" response is permitted. But please try to avoid this, by choosing the response that best describes just how affected your child has been over the last 3 months, and placing a tick-mark (√). On finishing, please check that you have answered all questions. The answers will be kept confidential to the clinic or research team.

All questions refer to the period of the last 3 months.

		FOR OFFICE USE ONLY
1. Over the last three months, taking everything into account, how has your child's health has been ?		
Very good	☐	
Good	☐	
Only fair, or poor	☐	
2. How many times has he/she had trouble with his/her ears ?		
Not at all	☐	
Once	☐	
2-3 times	☐	
4 or more times	☐	
3. How many ear infections has he/she had ? ***(i.e. severe pain in his/her ear, possibly with a temperature, smelly discharge in ear canal, or hole in eardrum)***		
0	☐	
1	☐	
2-3	☐	
4 or more	☐	

*. Exceptionally, the questionnaire can be used after a child becomes 9 years old (see User Manual)

All questions refer to the last 3 months.

		FOR OFFICE USE ONLY
4. How many times has he/she had an earache ?		
0	☐	
1	☐	
2-3	☐	
4 or more	☐	
5. How would you describe your child's hearing ?		
Normal	☐	
Slightly below normal	☐	
Poor	☐	
Very poor	☐	
Not sure	☐	
6. Has he/she mis-heard words when not looking at you ?		
No	☐	
Rarely	☐	
Often	☐	
Always	☐	
Not sure	☐	
7. Has he/she had difficulty hearing when with a <u>group</u> of people ? ***(ie not one-to-one)***		
No	☐	
Rarely	☐	
Often	☐	
Always	☐	
Not sure	☐	

All questions refer to the last 3 months.

		FOR OFFICE USE ONLY
8. How long can he/she concentrate on a game or a task <u>you have given him/her to do</u> ?		
Up to 2 minutes	☐	
Up to 5 minutes	☐	
5-10 minutes	☐	
10-15 minutes	☐	
More than 15 minutes	☐	
9. How often does he/she seek your attention unnecessarily ? ***(e.g. in an unusually dependent way, asking for help for a task he/she can do alone, demanding to be carried, demanding you play with them, following you around)***		
Less than once a month	☐	
Once a month	☐	
Once a week	☐	
Once a day	☐	
Two or more times per day	☐	
10. How often is he/she unhappy for no apparent reason ?		
Less than once a month	☐	
Once a month	☐	
Once a week	☐	
Once or more per day	☐	
11. Has he/she mispronounced the beginnings or ends of words ?		
No	☐	
Rarely	☐	
Often	☐	
Always	☐	
12. Has his/her speech been behind (less developed than) that of children of similar age ?		
No	☐	
A little	☐	
Moderately or a lot	☐	
Not sure	☐	

		FOR OFFICE USE ONLY
13. Have you often felt tired ?		
Yes	☐	
No	☐	
14. Has your child needed more attention than other children ?		
Yes	☐	
No	☐	

Responding person providing information

A. Would you describe your educational qualifications as:				Score 1
Left school before age 15 years	☐	Usual school exams for 15-16	☐	
Usual school exams for 17-18	☐	Further qualifications, but not university degree	☐	Score 2
University degree	☐	Not applicable	☐	

B. Are you:				Score 3
Child's mother	☐	Child's father	☐	
☐ Other (please specify).....				
Your own age.....| Age of child:.....				

C. If any impacts from the ear problems of your child which you think important have <u>not</u> been covered above, please mention up to 4 here:

1. .....

2 .....

3 .....

4 .....

Appendix 7 Serious adverse event report

Serious Adverse Event Case Report

Adverse incident

Female child aged 8 years admitted John Radcliffe Oxford with suspected acute mastoiditis

Details of event

27/3/2012	Otalgia R ear. Debris in canal. Treated with Otomize spray for otitis externa.
03/4/2012	Screened and diagnosed with bilateral OME (2 B-type tympanomgrams) . Presenting symptoms of hearing loss and snoring. Randomised to the Otovent group
13/4/2012	Otalgia initially resolved but returned in last 2 days. C/o stinging when using Otovent. Otovent stopped initially. Erythromycin antibiotic given.
14/4/2012	Out of hours - R ear sticking out abnormally. Redness behind ear and mastoid area. TM not seen as debris in canal. Diagnosed R Mastoiditis and referred to John Radcliffe paediatric - Kamran's Ward. Admitting surgeon Mr Mahmood Bhutta SpR in ENT. Consultant in charge Mr Grant Bates. Mastoiditis (mild/early) confirmed and child settled quickly on iv antibiotic

Medical History

9/2010	Pneumonia
2/2011	Chest infection referred to Paediatrician due to recurrent infections
12/2/2012	LRTI with asthma symptoms treated with erythromycin

Other Medication:

Cetirazine, clotimazole cream

Summary incident details

This is the first reported association of autoinflation with acute mastoiditis as far as we are able to determine. The incidence in the trial of acute mastoiditis in the treated group is 1 in 100 and 0 in 100 in the control group. If all clinical trial evidence is included (where quality reporting of adverse events is expected-Cochrane update) then there are about 350 in the treatment group, which together with our trial data gives a rate of 1 in 450. Epidemiology of comparator background incidence is available from the GPRD and suggests a background rate of approximately 1 in 2000 cases for acute mastoiditis (where there was otitis media in the previous 3 months). Apart from trial evidence Otovent is readily available over the counter and has been for over a decade. The manufacturer has not noted any serious adverse incidents with Otovent. The case has thus far been discussed with the DMEC, the chair of the TSC, The practice, the admitting ENT surgeon, and at an Expert Otitis Media Meeting in Oxford on April 24th. All relevant regulatory bodies are being notified.

The case was reported as mild by the admitting surgeon, the child made a rapid recovery on iv antibiotics without the need for surgery. Mr Ramsden the chair of the TSC stated that the actual clinical details of the case were very typical especially in relation to the time frame of the events starting with an URTI/Otitis Media and then progressing to acute mastoiditis at about 10 days. An expert microbiologist wondered if the case was an unusual infection e.g. mycoplasma but no microbiology was available.

Ascending infections are a theoretical possibility for an association but fewer such infections were found in the only previous small trial from the UK (Blanshard and Maw). The DMEC has data of middle ear infection episodes after randomisation on our trial database.

A single previously unreported event: *acute mastoiditis* associated with autoinflation, presents us with interpretive difficulties that would be clarified had we more data (a large sample from diverse quality sources). We have not established a clear theoretical mechanism in this instance, the technique involves pressure changes in the nose akin to doing the Valsalva manoeuvre but by using a balloon. There are some interesting details in the child's individual case record that suggest that she probably has a higher than average background risk of acute upper respiratory and serious infections.

Ian Williamson Chief Investigator AIR study 26th April 2012

Appendix 8 Qualitative interview guide

AIRS interview guide
6/2/2013

AIRS Parent Interview Guide

Brief: We are interested in your views and concerns , as a parent, about glue ear.

1. Can you describe your initial concerns about your child's health in relation to their ears and/or hearing?
   PROMPTS: How long? who by? seen the doctor? any treatment? Any concerns of your child? Adaptive strategies? Symptoms of most concern?

2. What were your thoughts about the possible impact of these problems?
   PROMPTS: observed any impact to date? Measures taken to limit impact?

3. How did you feel about the practice approaching you to check for glue ear in your child?
   PROMPTS: receiving a letter? Raised any concerns?

4. Can you tell me what happened when you first attended for screening?
   Prompts
   - Experience of tympanometry?
   - What were you told about the procedures?
   - Can you remember what questions you asked initially?
   - How quick and straightforward was the testing? Did it need repeating?

5. How did you feel when you received the results of the tympanometry?
   - How were the results explained to you? Were you shown a copy of the graph?
   - What is your understanding of what glue ear is?
   - What did you feel about receiving the diagnosis of glue ear and the impact this might have for your child?
   - Did this raise any further questions with you?
   - How acceptable was the technique to you and your child?

6. So the glue ear was confirmed and your child was randomised to receive the nasal balloon. Can you describe how the balloon was demonstrated to you and your child, and the first experiences of using it?
   Prompt
   - Did the nurse demonstrate. Was this helpful?
   - Did you use the balloon –how did it feel?
   - How did you feel that your child was managing at first? Did this change?
   - Using the balloon for 1-3 months is quite a long time. How did you find this?

7. How did you feel about the nasal balloon as a treatment for glue ear overall?
   Prompt
   - Acceptability as a treatment
   - Did you child like it?
   - Did you have any general concerns about the method or adverse events?

8. ***So the glue ear was confirmed and your child was randomised to the standard care group**. Can you describe what you understood by this?*
   PROMPTS
   - *Are you aware of active monitoring?*
   - *What concerns did you have at this stage?*
   - *Understanding of the natural course of the condition?*

9. After the end of the 3 month study did you child receive the nasal balloon?

10. Having taken part in this study you may be aware there are other treatments for glue ear, including antibiotics, oral steroids and surgery as well as the nasal ballon. Do you have any natural preferences towards any of these treatments? **PROMPTS: aversion?**

11. Can you describe your overall experience of participating in the trial?

End of the interview

AIRS Nurse Interview Guide

Demographic questions:

How long have you been qualified as a nurse? _____

How long have you been in your current position? _____

How many nurses are involved in research at your surgery? _____

How would you describe your research role at the surgery?

- Practice nurse fitting in research around other duties
- Research nurse with main duties of conducting research
- Research nurse from outside of GP practice
- Other _____

How many studies has the surgery been involved in during the past year? _____

Practice size _____

Practice location _____

Practice deprivation score _____

PCRN/CLRN _____

1. **Firstly, you attended a study training day at the outset of the study. Can you describe your experiences of the day?**
    - What else could have been covered?
    - Anything in more detail?
    - What was most helpful?

So after the training day you identified children to be screened for glue ear at your surgery? Can you describe the procedures that took place when the children came in for the screening visit?

Issues with tympanometry?

- How acceptable a technique do you consider tympanometry to be?
- Interpretation of tympanograms
- Support from the study team
- Support from within the practice – another nurse? GP?
- What sort of responses did you obtain from the children themselves?

2. **Can you describe how you explained the results to the parents?**
    - Did you use the graphs/printouts?
    - What further questions were raised from the parents at this stage?
    - What did you explain to the parents/children who did not meet the inclusion criteria/did not have glue ear? Parental concerns Expecting referral?

3. **For children randomised to the nasal balloon, can you describe what you did then?**
   Prompt
    - Did you demonstrate yourself?
    - What was the initial response by the parent and child?
    - How did they manage initially? Any strategies to help? Parents inflating balloon?
    - What were the reported experiences of using the balloon when they returned for follow up? Any longer term strategies?
    - General feelings about compliance? Predicting compliance
    - Interactions with the parents
    - Acceptability as a treatment
    - Did you have any general concerns about the method or adverse events?

4. **For children randomised to the standard care group. What did you think parents understood by this?**
    - What do you understand by active monitoring?
    - What sort of issues did parents raise at this stage?
    - Balloon may not be effective. In light of this what value would you give to active monitoring in primary care?

5. What did you do at the end of the study for the children whose glue ear had resolved? Not resolved?

6. **We are interested in whether a nurse-lead diagnostic service would be feasible in primary care.** What would your thoughts be in relation to
    - Benefits and value to the practice
    - Training
    - Support from the GPs
    - Impact on your time
    - Taking responsibility
    - Barriers
    - Potential impact at the GP practice level.
    - Impact on referrals?

7. **The study recruitment went very well. What do you think contributed to the recruitment success at your surgery?**

- Any barriers?
- Improvements?

8. **Can you describe your overall experience of taking part in the study**?

End of the interview

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