Paper:

Haggard, MP, Gannon, MM, Birkin, JA, Bennett, KE, Nicholls, EE, Spencer, H, Browning, GG, Georgalas, CDM, Bhutta, M, Higson, JM, Smith, SC, Hind, SE, Rovers, MM, Egner, EM, Hayman, T, Greenwood, DC, Carroll, RA, Jones, H, Richmond, TB, Wade, AR, Moorjani, P, Pearson, DAS, Kirk, G, Baskill, JL, Adams, DA, Toner, JG, Gibbin, KP, Jones, NS, Birchall, JP, Thomas, RSA, Narula, AA, Murty, GE, Griffiths, MV, Wilson, JA, Meikle, D, Johnson, IJM, Date, S, Kerr, AIG, Robinson, D, Madden, G, Bull, PD, Chapman, DF, Parker, AJ, Curry, AR, Williams, RG, Morrissey, MSC, Geddes, NK, Zarod, AP, Willatt, DJ, Proops, D, Pearman, K, Robb, PJ, MacKee, I, Law, K, Casey, M, Megarry, A, Smith, L, Smethurst, H, Pearce, G, Hook, P, Phipps, J, Gibbs, S, Dunster, S, Brown, E, Birch, EM, Page, V, Sim, A, Sharples, G, Crawford, J, Davies, C, Bartolo, J, Edwards, C, Wilson, J, Johnson, N, Baxendale, C, Welsby, W, Pickavance, N, Cox, V, Markham, K, Robb, JA, Flanagan, R, Housten, G, Jordan, G, Bingham, M, Cassidy, J, Burns, C, Hamill, C, Glover, L, Eccles, L, Armstrong-Bednall, G, Towle, B, Dyer, K, Carr, J, Herrod, J, Levick, A, Dunmore, P, Parker-Emery, C, Sutton, R, Gordon, C, Midgley, L, Barnett, N, Foley, R, Machlin, R, Elliott, C, Davidson, T, Walker, L, Keith, J, Brady, M, Barr-Hamilton, R, Wilson, S, McKenzie, J, Edgar, R, Noble, H, Thomas, H, Paul, B, Gilbert, M, Hoblyn, R, Walter, S, Griffiths, E, Inge, F, Hodges, M, Lawrence, C, Walsh, A, Loxley, T, Byrom, P, Walker, D, Najaran, R, Blyth, G, Mace, L, Rabaiotti, W, Trearty, C, Carmichael, A, Ronson, R, France, K, Pilkington, H, Hilton, F, Parsons, J, Whitby, G, Robinson, S, Brown, E, James, P, Allen, R and Study, MRCMOM (2012) *Adjuvant adenoidectomy in persistent bilateral otitis media with effusion: hearing and revision surgery outcomes through 2 years in the TARGET randomised trial.* Clinical Otolaryngology, 37 (2). 107 - 116. ISSN 1749-4478

http://dx.doi.org/10.1111/j.1749-4486.2012.02469.x

Adjuvant adenoidectomy in persistent bilateral otitis media with effusion: hearing and revision surgery outcomes through 2 years in the TARGET randomised trial

MRC Multicentre Otitis Media Study Group*

MRC Scottish Section Institute of Hearing Research, Glasgow, UK

Abstract

Objectives: To determine the adjuvant effects of adenoidectomy with short-stay ventilation tubes to hearing and revision surgery in children over 3.5 years with persistent otitis media with effusion.

Design: Randomised controlled three armed trial: observation, short-stay ventilation tube or ventilation tubes with adjuvant adenoidectomy. Five follow-up visits over 2 years.

Setting: Eleven UK Otorhinolaryngology Departments.

Participants: Children with bilateral otitis media with effusion and better ear hearing level (HL) ‡20 dB persistent for 3 months. Of the 425 eligible children, 376 (88%) accepted randomisation.

Main outcome measures: Pure-tone hearing thresholds, eligibility for and actual revision surgery rates, otoscopic sequelae and complications of adenoidectomy.

Results: Loss to follow-up at 3, 12 and 24 months was 2%, 6% and 5% respectively. Of the 376 randomised children, 253 (67%) had complete data for all five follow-up visits. Adenoidectomy did not add to the benefit to hearing thresholds of ventilation tubes of 8.8 dB (CI: 7.1–10.5) averaged over 3–6 months postoperatively. Averaged over 12, 18 and 24 months, adenoidectomy provided 4.2 dB of benefit (CI: 2.6–5.7) whilst ventilation tubes gave no benefit. Standardised effect sizes through two years showed equal benefit from ventilation tubes (0.50 sd) and adenoidectomy (0.61 sd) which are additive (1.11 sd). Adenoidectomy halved the numbers meeting a 25 dB HL bilateral cut-off for eligibility for repeat tube surgery from 31% to 14% at 12 months and from 33% to 15% at 18 months. The actual reduction in re-insertion surgery (absolute risk difference) was 21%. In tubed ears, tympanosclerosis occurred in 27%, but otorrhoea in only <2% and permanent perforations in <1%. These events did not occur in control ears. In children that had adenoidectomy, one of 165 (0.6%) had haemorrhage that required return to theatre.

Conclusions: Adjuvant adenoidectomy doubles benefit from short-stay ventilation tubes by extending better hearing through the second year in children aged 3.25–6.75 years with persistent otitis media with effusion with at least a 20 dB HL in both ears. The duration of benefit of adenoidectomy is related to the duration of function of the type of the ventilation tubes used. Adenoidectomy also substantially reduces eligibility for revision surgery.

Otitis media with effusion is the overriding cause of hearing loss in early and middle childhood with high associated healthcare expenditure. The condition is largely self-limiting, leading to much debate over justifications for surgery and to wide national and international variation in intervention rates. Affected children may be surgically treated by ventilation tube (VT) placement, also known as grommets or tympanosotomy tubes, with or without adjuvant adenoidectomy (+ad).

The benefit from short-term VTs alone to hearing has been adequately shown in an individual patient metaanalysis [1] and a Cochrane systematic review.2 Both of these included raw data from the MRC funded Trial of Alternative Regimens in Glue Ear Treatment (TARGET). However, the magnitude of the hearing benefit of VTs is small and limited to the duration of tube patency.[2] Hence, the NICE guideline[3] recommended that only 'children with persistent bilateral OME documented over a period of 3 months with a hearing level (HL) in the better ear of 25–30 dB HL or worse should be considered for surgical intervention'.

The adjuvant role of adenoidectomy to VTs was one of the main reasons why TARGET was funded as previous adenoidectomy trials had conflicting evidence of benefit to hearing and reduction in revision surgery rates.[4,5] Because of the inconsistent evidence, NICE restricted its recommendation of adenoidectomy to children with co-present severe or persistent upper respiratory tract infection. However, a recent trial has shown that these are themselves not indications for adenoidectomy.[6]

This paper reports the adjuvant effects of adenoidectomy, along with short-stay VTs, to hearing thresholds and revision surgery in children over 3.5 years with persistent OME.

Methods

Recruitment took place between April 1994 and January 1998 in 11 UK ENT departments (Fig. S1). Generalisability of the trial sample in relation to the referred clinical caseload has been examined in some detail[7] but the trial protocol is summarised in the CONSORT flow diagram (Figs 1 and S1).

Eligibility criteria

Included children were aged 3¼–6¾ years on a first visit with no previous ear surgery and had on two qualifying visits, three months apart: a bilateral B + B or B + C2 tympanogram combination (modified Jerger),[8] and better ear HL >= 20 dB HL averaged across 0.5, 1, 2 and 4 kHz and air–bone gap > 10 dB.[9] Non-independence of these markers entails that the conjunction is not greatly more stringent than the 20 dB HL component alone.

At discretion of the consultant (Appendix S1), children with poorest HLs (binaural HL > 40 dB HL) could be treated (i.e. not randomised) yet followed up. Another 42 also

with binaural HL > 40 dB HL remained in the randomised group and are included in the intention-to-treat analysis.

All included children were followed up over five visits at 3, 6, 12, 18 and 24 months post-randomisation.

Ethical considerations

The Trial was approved by the local research ethics committees for each centre as well as the appropriate multicentre research ethics committees for England, Wales, Scotland and N. Ireland.

Interventions

Eligible children with parental consent were randomised to one of three interventions:

1 Bilateral Shepard VTs (http://www.invotec.net/ventilation_tubes.html) following myringotomy and fluid aspiration (VTs).

2 Ventilation tubes with adjuvant adenoidectomy (VTs +ad).

3 Further watchful waiting (FWW).

All children receiving surgery received it within 6 weeks of randomisation and most within 4 weeks, where different from allocation this was extracted from the surgical notes.

Outcome measures

Hearing levels. Air conduction thresholds at 0.5, 1.0, 2.0 and 4.0 kHz in each ear at every visit were summarised as the 4-frequency average binaural hearing thresholds for comprehensiveness and reliability.9 To reliably adjust treatment arm comparisons post-randomisation, the baseline HL was taken as the period average over the two qualifying visits.

Revision surgery. If at any follow-up visit, the surgeon and the parent after perusing the current hearing thresholds, tympanometry and otoscopy felt that revision surgery was indicated and this was recorded. The type of revision surgery was later documented and follow-up was as per protocol. No strict eligibility criterion was laid down to allow surgeon／parent discretion, but the implication was that the children should have bilateral OME with a hearing impairment of at least 20 dB HL in both ears. Children that had revision surgery were analysed at the time intervals related to their initial surgery.

Otoscopy. At each visit, the ears were examined by the consultant otologist using an otoscope, supplemented by otomicroscopy where necessary. The findings (discharge or other otoscopic suspicion of infection, perforation and tympanosclerosis) were recorded on a summary data sheet with prompt categories and schematic left and right eardrum diagrams (Appendix S1). The otoscopic findings are reported on an 'as treated' basis and thus include children that transferred to surgery from FWW.

Sample size. To address sustained benefits from adenoidectomy, a 3 dB difference averaged over 12, 18 and 24 months was postulated as small yet worth knowing about; this would capture the cumulative functional consequence of lesser disease recurrence. Given the known variability of measurement, for alpha 0.01 with 80% power, this needed equal group sizes of 110. Recruitment beyond this would assist supplementary aims for interactions and for overall effects on other outcomes of policy relevance, for which power calculation in advance was not feasible.

Randomisation. Randomisation was performed by telephone call from the nurse／research assistant to the statistician at the MRC Institute of Hearing Research and allocation immediately communicated to the parent.

Sequence. For each centre, the first five children were randomised according to a computer generated random number sequence. Thereafter, the minimisation procedure 10 balanced the treatment allocations across four dichotomous factors: boy, girl; £5.25, >5.25 years old at initial visit; manual, non-manual occupation of head of household and baseline hearing £25 dB HL, >25 dB HL. This basis of minimisation was not divulged to centres and may be regarded as completely concealed. The process produced 122 (FWW), 126 (VTs) and 128 (VTs +ad) cases.

Blinding and bias. Audiometry was performed by audiologists, independently of the otolaryngologist and research nurse. Clinic pressures meant that these testers, whilst not blinded in the strictest sense, were not aware of the child's allocation, nor in a position to be influenced by such information were it present. True HLs are unlikely to be affected by the parent's or child's knowledge of the intervention in a surgical trial.

Statistical methods

Analysis strategy. All analyses were by-child and as-randomised ('intention-to-treat'), except where otherwise stated. We defined two natural summary periods for outcome imputation: 3 plus 6 months when initial VTs are mostly still functioning, and 12, 18 and 24 months, when they are not.[11]

The appropriateness of this was confirmed by two non-imputed trajectories on cases with all visits present by: (i) maximum cases, with the given variable present for the particular visit, and (ii) complete cases, all having the given variable present at baseline and every follow-up visit. For unbiased effect estimation, general linear models (multiple regressions) predicted the continuous measures of outcomes from

two terms: the same variable at baseline (main-effect) and randomised treatment allocation, a three-level categorical term. Further models including baseline treatment interactions were also run, only briefly reported here. All models used imputation for missing data on first, second or combined periods. Where necessary, square root or logarithmic transformations were used to normalise residuals; as these also homogenised variance, standardised treatment effect sizes (TES) used SDs from pooled (three-arm) error estimates.

Results

Baseline characteristics and adherence to allocated management

Randomised group characteristics show no material or reliable difference, in any of the demographic or traditional risk factor variables between groups (Table 1).

Over the 2-year follow-up period, 98 children (26%) transferred to a non-allocated group (Fig. S1), mostly in the first year. The limited acceptability of FWW is shown by 69 (57%) children transferring from it to active treatment, with only 53 (43%) of FWW not ultimately receiving surgery; the wider methodological implications of such high transfer rates are considered more fully in a later paper. Among the 29 other transfers, only three were from surgery to FWW, the majority (later) receiving adjuvant adenoidectomy with re-insertion. As treated at 2 years, 53 had received FWW, 146 VTs and 165 VTs +ad (Fig. S1). Loss to follow-up was no higher in the FWW children (FWW 21; VTs 17, VTs +ad 20) suggesting that any transfer to surgery outside the National Health Service was negligible if any.

Overall HL trajectory

The HL trajectories for complete data cases (N= 253) and for all cases seen at each visit (Fig. 2) confirm effects of randomised VTs lasting less than one year for VTs, but at least 2 years with additional adenoidectomy, hence the basis of analysis (and imputation) in the two contrasting periods. At 1 year, most tubes (82%) are extruded or non-functioning.[11] Transfers eliminate any advantage for VTs thereafter but the disadvantage (NS) seen is because of lag not harm. The HLs are then strikingly stable, with the 12, 18 and 24 month means for FWW and VTs differing by only 0, 1.2 and 0.1 dB, respectively, and with VTs +ad consistently showing a 4 dB advantage (Fig. 2 and Table S1).

Hearing level in early and late follow-up

Table 2 shows the HL for all randomised cases, aggregated for each follow-up period. In the first 6 months, VTs confer large (TES = 1.28) and significant ($P < 0.001$) benefit to HL, but overall, adenoidectomy does not enhance this when the VTs are mostly patent (i.e. treatment benefits appear subadditive). The 2nd year

imputed data show VT and FWW with similar HLs, but the +ad overall benefit is able to emerge (P< 0.001), with +ad conferring a 4.2 dB (CI: 2.6–5.7 dB) benefit and no significant diminution over time. Over the combined 2-year period, the advantage in HL from +ad over VTs alone is also significant (P< 0.001). This longer duration of adenoidectomy benefit makes the 2-year contributions of VTs and +ad to HL complementary in time, and of broadly similar magnitude, (2-year TES = 0.50 sd for VTs alone; 0.61 sd for +ad), consistent with the similar areas separating pairs of lines in Fig. 2.

Indicator role for baseline severity

No significant correlation was found between the benefit to HL from VTs ± adenoidectomy to the HL baseline.

Revision surgery and its relation to HLs

No formal criterion for revision surgery was imposed by the protocol, so the essentially continuous HL data are reformulated as hypothetical eligibility criteria of 20, 25 or 30 dB HL (Table 3). Compared with the VT group, fewer children in the VTs +ad group met these criteria in all analysis. At 3 months, no difference would be expected, when most tubes were functioning. Over 12, 18 and 24 months, 35% (CI: 26–43) of 115 children in the VT group attending these visits versus 13% (CI: 7–19) of 115 in VTs +ad group re-met a 25 dB HL cut-off, making children in the VTs alone group more likely by about threefold (RR 2.7; CI: 1.6–4.6) to re-qualify for surgery than those receiving VTs +ad.

Three months following randomisation, in 42% (CI: 33–51) of 106 children in the non-surgical arm with data at this point, the OME had resolved sufficiently that they no longer met the >=20 dB HL entry criterion. Imposing such dichotomous criteria exaggerates short-term systematic (e.g. seasonal) and random fluctuation; only 47% of these short-term resolvers (i.e. 21 children) then remained below 20 dB in at least one ear through 2-year follow-up.

Through follow-up, clinicians had audiometric data available for clinical review and re-insertion was discretionary; 78% of children then selected for reinsertion did in fact re-meet the 20 dB HL trial entry criterion. Of the 126 randomised to VTs only, 38 (30%) received revision surgery, compared with 12 (9%) of the 128 children randomised to VTs +ads (RR = 3.2; CI: 1.8–5.9). Of those who would have met a 25 dB better ear HL eligibility criterion in the second year of trial, 58% in the VTs group versus 40% in the VTs +ad group underwent revision surgery (RR = 1.4; CI: 0.8–2.4). Thus, HL was the main driver of repeat surgery and the contribution of

adenoidectomy to meeting HL cut-off largely explains its reduction of further surgery – a different manifestation of the same outcome.

Adverse effects

Of 635 ears that had a VT inserted, eight had a perforation at visit 7 that was recorded at least 6 months after any surgery. Subsequent record search showed that in the four who attended a post visit 7 appointments, all had healed. Similarly, six of seven perforations recorded at visits 5 or 6 and that could be checked at a subsequent visits had resolved. Lasting perforations are therefore rare but at worst there could be as many as 0.8% (5⁄635). Tympanosclerosis was seen in 20% (128 of 635) ears versus none in un-operated ears. The incidence of infection associated with VT insertion was low: only 43 ears (7%) showing it at any point over follow-up.

One of the 165 (0.6%) children that had adenoidectomy had to return to theatre for postoperative haemorrhage. The trial was not designed to pick up other rare complications of adenoidectomy including velo-pharyngeal incompetence.

Discussion

Synopsis of key findings

In children aged 3.25–6.75 years with persistent bilateral OME with a HL of at least 20 dB HL in both ears;

1. Where times are in common, TARGET results for VTs alone are similar to those in other trials and meta-analyses.[2] The average audiometric benefit to the hearing thresholds from VTs of 8.8 dB re-controls (CI: 7.1–10.5) for the period centred on 3–6 months post-randomisation disappeared by 12 months.
2. Adenoidectomy with VTs extends benefit to hearing through the second year without evident diminution; the magnitude of this benefit was 4.2 dB HL (CI: 2.6–5.7) over VTs alone. As a result in the combined operation, adenoidectomy contributes approximately as much to hearing over 2 years as VTs do.
3. Adjuvant adenoidectomy reduces audiometric eligibility for revision surgery and actual surgery rates; 34% of VTs group versus 13% of VTs +ad group met the 25 dB HL cut-off at some point over the second year of follow-up, giving an absolute risk reduction of 21%.

Strengths of the study

TARGET is the only by-child RCT of VTs +ad in the age groups of 3.7–7 years having bilateral persistent OME (i.e. with a HL of 20 dB or greater in both ears over 3 months). The children came from the NHS primary to secondary referral healthcare system and were at the more severely affected end of the clinical distribution, after a sixfold reduction of referrals by watchful waiting within the entry criteria.[7] Second

year outcomes, particularly relevant to the contribution of adenoidectomy, were thoroughly documented. The findings can thus be strongly generalised to selective policies for secondary care case-loads in countries with restrictive prior referral and similar entry criteria, but not to substantially younger or less selected caseloads.

For HL, complete data on all seven visits were available for 67% of children, on at least one of the 3 and 6 months visits in 94%, and on at least one of the 12-, 18-, and 24-month visits in 91%. The use of imputation adjusts for any attrition biases, which were not removed in previous OME trials, but the degree of difference that this can make was limited because of the reasonably high follow-up rate here and to established absence of pointers to large bias such as particularly favourable or unfavourable results just prior to missing data.

Limitations of the study

The follow-up schedule did not include 9 months, which could have given more information on the emergence of an advantage for adenoidectomy, the duration of VT benefits and optimum schedule for review on recurrence. It would also have been beneficial to have had follow-up beyond 24 months to determine the duration of additional benefit from adenoidectomy. Data on clinical reasons for re-insertions supplementary to hearing could have documented practice and clinical belief, perhaps suggesting supplementary indicators for interaction tests with hearing and other outcomes.

The high proportion of cases transferring from further watchful waiting to surgical management at 6 months will affect the overall hearing outcomes from surgery, on an intention-to-treat analysis, but there is no reason to expect this to be different between tubes alone and tubes with adenoidectomy. Hence, comparisons between VTs alone and adenoidectomy in addition to tubes which are the novel aspect of this paper are not likely to be influenced by transfers from the control arms to surgery.

Comparison with other studies

Three previous trials 4,12,13 randomised children to have or not have adenoidectomy and one ear but not the other to have a VT inserted. Eligible children were comparable to those in TARGET in age range, persistence of bilateral OME with a defined >20 dB HL. Adenoidectomy had an additional benefit to hearing of 2 dB at 6 and 12 months.[5]

To date, the benefit in the second year after adenoidectomy has not been reported. The current study shows the benefit of adenoidectomy in the second year to be of a similar magnitude to hearing as VTs do in the first year.

Previous trials have shown a reduction in repeat operations of about a third of children having adenoidectomy[4] with varying degrees of OME. However, revision surgery frequently takes place for multiple reasons, and the parents of many children with persistent OME do not want their child to have a further operation. This study overcomes these biases by reporting the audiometric eligibility for revision surgery at various audiometric levels. The reduction achieved by adenoidectomy of 31–14% at 12 months and from 33% to 15% at 18 months using a 25 dB HL cut-off is chosen as that is the level in the current NICE guidelines.[3]

Tympanosclerosis and otorrhoea are well-recognised sequelae of VTs, and TARGET's prevalence of these is in keeping with meta-analysis by Kay et al.[15] However, the 'maximum' incidence of chronic perforation of 0.8% is lower than Kay et al.'s figure of 2.2% (CI: 1.8–5.0) for short-term tubes. The most likely reason for this is that the incidence of otorrhoea in TARGET was low because OME rather than recurrent acute otitis media was the rational for tympanostomy. A less likely alternative is a difference in VT design or material.

Policy implications

In children with relatively severe and persistent bilateral OME distribution, there is a significant benefit of about 9 dB from short-stay VTs alone, when averaged over 3 and 6 months. At 1 standard deviation of the outcome measure distribution, this meets the general criterion for a statistically large effect, and a similar magnitude is seen through 2 years if adjuvant adenoidectomy is also performed. The result need not be seen as surprising when prior selection by the entry criteria removes the non-persistent five sixths of the referred caseload. The trade-off between benefits and risks or side-effects, comparing longer-stay tubes with adjuvant adenoidectomy, is certainly complex and has never been comprehensively addressed. What is lacking is quality information of duration of tube function for alternative tubes.[14] Other types of tubes were to function for a longer period of time that might lessen the proportion of time in the second year that a child would benefit from adenoidectomy. However, the majority of children do not need their middle ear ventilated for longer than with a Shepard tube. For them, longer-stay tubes would be both unnecessary and result in more frequent sequelae.

Showing advantage for one strategy does not remove the need to consider the other, but if adenoidectomy is shown to benefit general health in OME, the attractiveness of longer-stay tubes would be less.

The extension of hearing improvement with adenoidectomy and the reduced number of children receiving repeat surgery appear closely related. The absolute risk reduction of re-insertion by 21% is substantial for the case type entering and can be set against the increased risk of adenoidectomy. A 100% adjuvant adenoidectomy rate in persistent OME is not appropriate on grounds of logistics (scheduling of operating list) or the risk of haemorrhage, even if offset by the reduced risk of re-insertion, so cost-effectiveness analysis on the entire VTs +ad arm would be too crude to be informative. The concentration of the present average benefits into definable subgroups for the respective treatment components therefore has high priority. Recommendations on surgery in children over three and a half years should address the joint and complementary deployment of the two operations, and routine hospital activity data should henceforth distinguish this definite adjuvant role in OME from other reasons for adenoidectomy in children.

Acknowledgements

Prof M P Haggard (epidemiologist); Dr J.M. Higson (audiologist) and Ms Helen Spencer (statistician) are thanked in particular for finalising the data and help with writing this version of the manuscript.

Conflict of interest

None to declare.

References

1 Rovers M.M., Black N., Browning G.G. et al. (2005) Grommets in otitis media with effusion: an individual patient data meta-analysis. Arch. Dis. Child. 90, 480–485.

2 Browning G.G., Rovers M.M., Williamson I. et al. (2010) Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database of Syst. Rev. CD001801. DOI: 10.1002/14651858.CD001801.pub3.

3 National Institute for Clinical Excellence. (2008) CG60 Surgical management of otitis media with effusion in children. URL http://www.nice.org.uk/nicemedia/pdf/cg60fullguideline.pdf.

4 Maw A.R. & Bawden R. (1994) Does adenoidectomy have an adjuvant effect on ventilation tube insertion and thus reduce the need for re-treatment? Clin. Otolaryngol. Allied Sci. 19, 340–343.

5 Freemantle N., Sheldon T.A., Song F. et al. (1992) The Treatment of Persistent Glue Ear in Children. Effective Health Care Bulletin No. 4. University of York, NHS Centre for Reviews and Dissemination, New York.

6 Van den Aardweg M.T.A., Boonacker C.W.B., Rovers M.M. et al. (2011) Effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections: open randomised controlled trial. Br. Med. J. 343, d5154.

7 MRC Multi-centre Otitis Media Study Group. (2001) Surgery for persistent otitis media with effusion: generalizability of results from the UK trial (TARGET). Trial of Alternative Regimens in Glue Ear Treatment. Clin. Otolaryngol. 26, 417–424.

8 MRC Multi-centre Otitis Media Study Group (2008) An extension of the Jerger classification of tympanograms for ventilation tube patency specification and evaluation of equivalent ear-canal volume criteria. Ear Hear. 29, 894–906.

9 MRC Multi-centre Otitis Media Study Group. (2000) Influence of age, type of audiometry and child's concentration on hearing thresholds. Br. J. Audiol. 34,231–240.

10 Pocock S.J. (1983) Clinical Trials: A Practical Approach. Wiley, Chichester.

11 MRC Multi-centre Otitis Media Study Group. (2003) The role of ventilation tube status in the hearing levels in children managed for bilateral persistent otitis media with effusion. Clin. Otolaryngol. 28, 146–153.

12 Black N.A., Sanderson C.F., Freeland A.P. et al. (1990) A randomised controlled trial of surgery for glue ear. Br. Med. J. 300, 309–315.

13 Dempster J.H., Browning G.G. & Gatehouse S.G. (1993) A randomised study of the surgical management of children with persistent otitis media with effusion associated with a hearing impairment. J. Laryngol. Otol. 107, 2849.

14 Browning G.G. (2008) Otitis Media With Effusion in Scott-Brown's Otorhinolaryngology and Head and Neck Surgery, 7th edn, Chapter 72. 896.

15 Kay D.J., Nelson M. & Rosenfeld R.M. (2001) Meta-analysis of tympanostomy tube sequelae. Otolaryngol. Head Neck Surg. 124, 374–380.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Fig. 1. Consort diagram showing pathway of the children through the 3-month qualifying period (three visits) and the 24-month follow-up period (five visits).

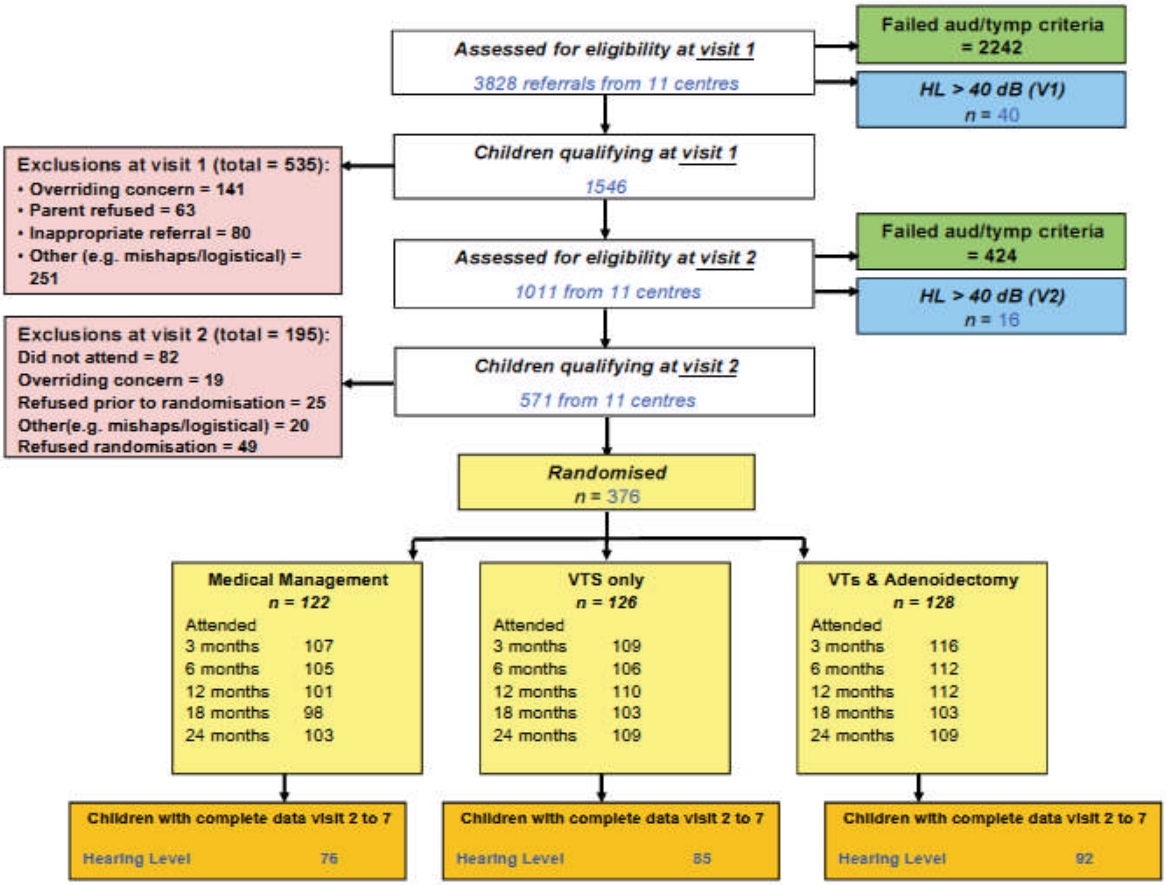


Table 1: Baseline characteristics of 376 randomised children.

	Further watchful waiting N = 122	VTs N=126	VTs +ad N=128	Total N=376	Missing %	P-value	
Age at randomisation in months							
Mean (sd)	62.9 (10.4)	62.5 (10.2)	64.5 (10.3)	63.3 (10.3)	0	0.27	
Gender %							
Male	51	48	48	49	0	0.91	
Socio-economic group %							
Manual	67	67	65	66			
N	122	126	125	373	0.8	0.92	
Ethnic group %							
White	96	98	95	96			
Afro-Carib			1				
Indian-Pakistani	3	2	3	3			
Other	1		1	1			
N	122	126	125	373	0.8	0.78	
Season when randomised							
Winter (January–March)	36	26	28	30			
Spring (April–June)	27	33	35	32			
Summer (July–Sept.)	20	26	18	21			
Autumn (October–Dec.)	17	14	19	17			
N	122	126	128	376	0	0.35	
Mean hearing level dB HL (sd)							
Visit 2	33.5 (6.4)	32.2 (6.0)	31.7 (6.4)	32.4 (6.3)	0	0.07	
Av visits 1 and 2	33.8 (4.8)	33.2 (4.6)	32.8 (5.2)	33.2 (4.9)	0	0.24	

Mean reported hearing difficulty – RHD (sd)						
Visit 2	13.6 (4.5)	14.4 (4.1)	14.0 (4.2)	14.1 (4.3)		
N	110	122	120	352	6.4	0.63
Av visits 1 and 2	13.2 (4.1)	13.9 (3.8)	13.6 (3.8)	13.5 (3.9)		
N	122	126	127	375	0.3	0.39
Other siblings with OM						
Yes	83	83	88	84		
N	122	126	127	375	0.5	0.39
Acute otitis media episodes %						
> 6 per year	7	4	4	5		
N	122	126	127	375	5.6	0.54
Attended daycare %						
Yes	100	98	100	99		
N	110	123	120	353	6.1	0.06†
Mother smokes %						
Yes	29	32	40	34		
N	101	110	115	326	13.3	0.19

† Low numbers not attending daycare suggest the marginally significant result is unreliable.

Fig. 2. Time course of hearing level (HL). Mean HL and 95% CIs of the HL scores for complete data (n = 253) are compared with those for maximum data available in the 376 randomised children.

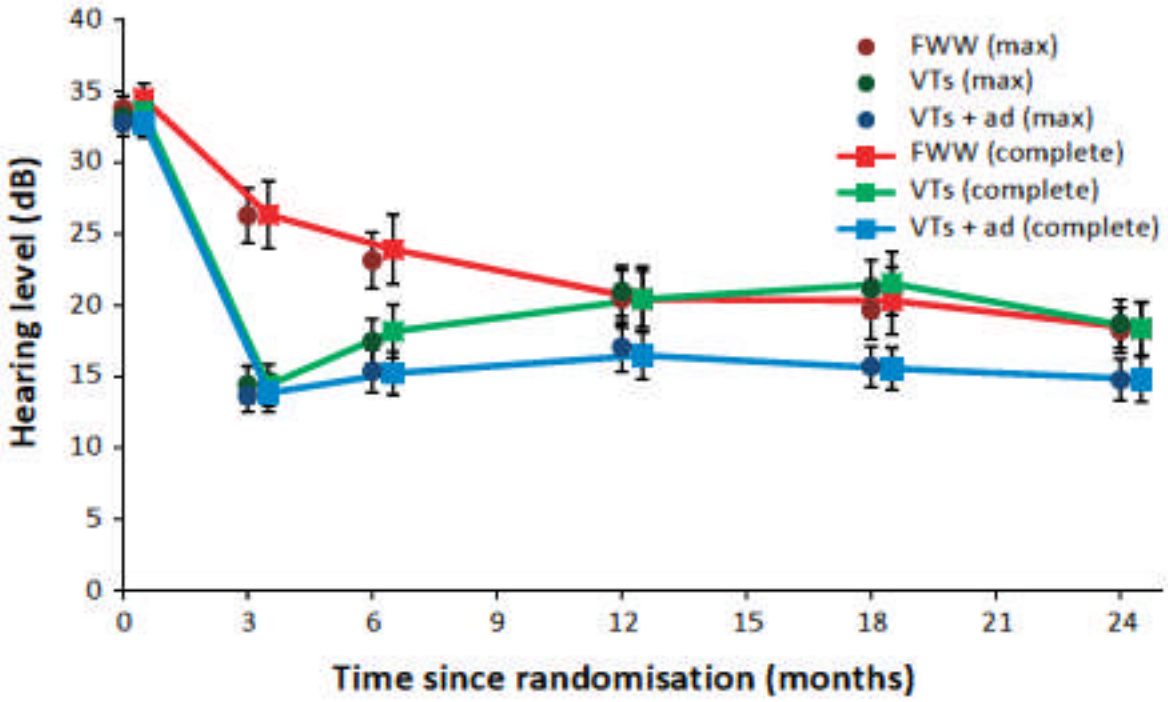


Table 2. Descriptives and standardised treatment effect sizes (TES) in sd for hearing levels (HL), for the two follow-up periods and combined, and TESs for the same contrasted between measures. The two treatment groups are each specified relative to further watchful waiting (FWW) controls

	HL Mean	sd	CI	TES*
3 and 6month visit average				
VTs	15.9	6.2	14.8, 17.0	1.28
VTs +ad	14.6	6.1	13.6, 15.7	1.50
FWW Ctrls	24.7	7.7	23.3, 26.1	Difference 0.23†
12, 18, 24 months visit average				
VTs	20.1	6.5	19.0, 21.2	-0.14‡
VTs +ad	15.9	5.9	14.9, 17.0	0.55
FWW Ctrls	19.4	6.2	18.3, 20.5	Difference 0.69
2-year combined period average§				
VTs	18.5	5.2	17.6, 19.5	0.50
VTs +ad	15.5	5.3	14.5, 16.4	1.11
FWW Ctrls	21.4	5.6	20.4, 22.4	Difference 0.61

Values are imputed for missing data, giving complete as randomised Ns of 122, 126 and 128, respectively, for FWW, VTs and VTs +ad. The means, SDs, CIs given here are raw but the TESs are based on distributions transformed to normality as for statistical tests. The TES for a sum or difference is close to, but cannot be precisely deduced from, those entailed by its parts; this is because of correlation affecting the variance for the sum or difference.

* Standardised treatment effect size. This is the ratio of the mean difference between the two treatment groups in question to the pooled sd in the as-randomised analyses.

† This and all other italicised entries are not for FWW, but for the differences in TES of the two treatment regimens in rows above.

‡ Negative value (NS) occurs because in this period more of the control group have transferred to treatment, and so have functioning VTs, than is seen in the surgery groups where VTs have mostly fallen out.

§ Weighted as 9 : 15 for the numbers of months in which the follow-up visits are centred, with 3 months' margin at boundary, e.g. 3- and 6-month measures centre on 0–9 months.

Table 3. Eligibility rates for revision surgery as defined for 20, 25 and 30 dB cut-offs in HL, for the 254 children randomised to surgery in TARGET

Visit	Allocated group	% with HL>20 dB	% with HL>25 dB	% with HL>30 dB	N	Fisher exact test for HL >25 dB P-value	Relative risk
3	Vts	7	4	2	109	>0.1	
	Vts +ads	8	3	2	116		
4	Vts	18	8	7	111	>0.1	
	Vts +ads	10	7	3	114		
5	Vts	31	16	10	110	0.039	2.3
	Vts +ads	14	7	4	111		
6	Vts	33	18	13	103	0.001	4.8
	Vts +ads	15	4	2	103		
7	Vts	26	15	6	108	0.026	2.7
	Vts +ads	17	6	1	109		
Any of 5,6,7	Vts	61	40	26	115	<0.001	2.7
	Vts +ads	37	15	7	115		

Appendix 1: authorship list for MRC Multicentre Otitis Media Study Group

IHR Scientific/Medical Staff: Project Leader – Haggard MP; Health Services Researcher/Trial Co-ordinator – Gannon MM; Co-ordinator – Birkin JA; Statisticians – Bennett KE, Nicholls EE, Spencer H; Lead Academic Clinician – Browning GG; affiliated. ENT trainees: Georgalas C Daniel M, Bhutta M. Audiological Scientist – Higson JM; Psychologists – Smith SC, Hind SE; Epidemiologist – Rovers MM.

IHR Support Staff: Data Manager – Egner EM; Research Assistants – Hayman T, Greenwood DC, Carroll RA, Jones H, Richmond TB, Wade AR, Moorjani P, Pearson DAS, Kirk G; Audiologist – Baskill JL.

RCT centres: Royal Victoria Hospital, Belfast; Ulster Hospital, Dundonald; University Hospital, Nottingham; Leicester Royal Infirmary, Leicester; Royal Hospital for Sick Children, Bristol; Freeman Hospital, Newcastle; Royal Hospital for Sick Children, Edinburgh; Queen Alexandra Hospital, Portsmouth; Sheffield Children's Hospital, Sheffield; Coventry and Warwickshire Hospital, Coventry; University Hospital of Wales, Cardiff.

Other contributing centres: Royal Hospital for Sick Children, Glasgow; Manchester Children's Hospitals; Diana, Princess of Wales and Heartlands Hospitals, Birmingham; Epsom General Hospital, Epsom; Sunderland Royal Hospital, Sunderland; Tyrone County Hospital, Omagh.

We acknowledge the contribution of all the hospital chief executives, medical directors, clinical managers and pharmacists in facilitating the trial.

Collaborating Consultants: Adams DA; Toner JG; Gibbin KP, Jones NS, Birchall JP; Thomas RSA, Narula AA, Murty GE; Griffiths MV; Wilson JA, Meikle D, Johnson IJM, Date S; Kerr AIG; Robinson D, Madden G; Bull PD, Chapman DF, Parker AJ; Curry AR; Williams RG; Morrissey MSC, Geddes NK; Zarod AP, Willatt DJ; Proops D, Pearman K; Robb PJ; MacKee I; Law K.

Nurses/Research Assistants: Casey M; Megarry A; Smith L, Smethurst H; Pearce G, Hook P, Phipps J; Gibbs S, Dunster S; Brown E, Birch EM, Page V; Sim A; Sharples G, Crawford J; Davies C; Bartolo J; Edwards C; Wilson J, Johnson N; Baxendale C, Welsby W, Pickavance N; Cox V, Markham K; Robb JA.

Audiological Scientists/Audiologists: Flanagan R, Housten G, Jordan G, Bingham M, Cassidy J; Burns C, Hamill C, Glover L, Eccles L; Armstrong-Bednall G, Towle B, Dyer K, Carr J, Herrod J, Levick A; Dunmore P, Parker-Emery C, Sutton R, Gordon C; Midgley L, Barnett N, Foley R, Machlin R; Elliott C, Davidson T, Walker L, Keith J; Brady M, Barr-Hamilton R, Wilson S, McKenzie J, Edgar R, Noble H; Thomas H, Paul B, Gilbert M, Hoblyn R, Walter S, Griffiths E, Inge F; Hodges M, Lawrence C, Walsh A, Loxley T, Byrom P; Walker D, Najaran R, Blyth G, Mace L; Rabaiotti W; Trearty C, Carmichael A; Ronson R, France K, Pilkington H; Hilton F, Parsons J; Whitby G, Robinson S; Brown E, James P; Allen R.

Figure S1.

Fuller CONSORT diagram for TARGET study.

Table S1.

Mean HL (standard deviation) at baseline and at each visit up to end of 2-year follow-up.

Appendix S1.

Otomicroscopy Coding Form.

Web appendices

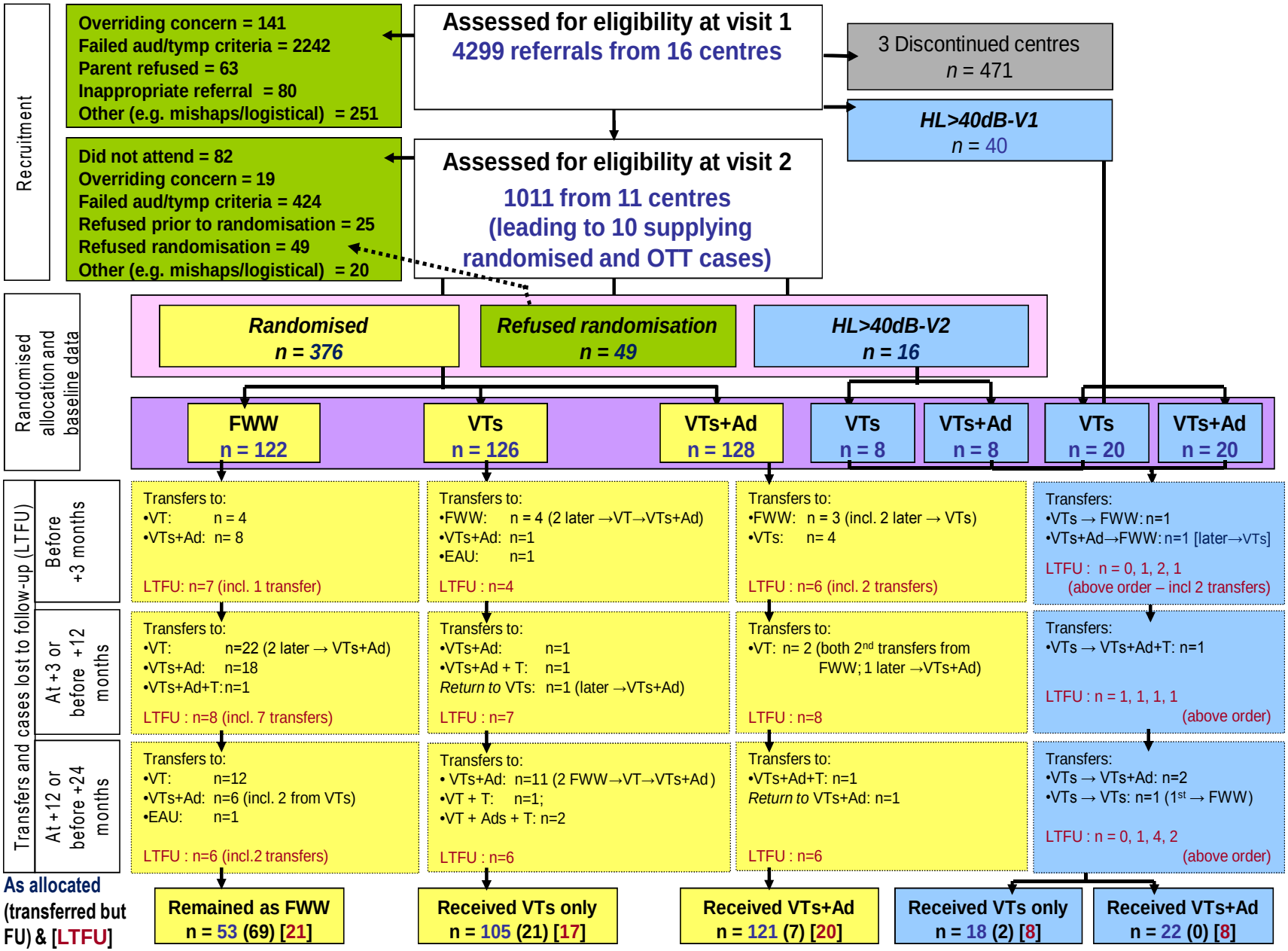
Figure S1. Fuller CONSORT diagram

Appendix S1. Otomicroscopy coding form

Table S1. Mean HL (standard deviation) at baseline and at each visit to end of 2-year follow-up. Data are presented for (i) maximum number of cases available and (ii) for cases having complete data across all visits. HL data are displayed in Figure 2.

Figure S1: Fuller CONSORT diagram for TARGET study

S1: Fuller CONSORT diagram for TARGET study



Notes to support interpretation of CONSORT diagram

1. Abbreviations: FWW = Forward watchful waiting ie non-surgical controls;
   VTs= Ventilation Tubes (aka grommets, tympanostomy tubes, pressure equalisation tubes (PETs));
   VTs+Ad= Ventilation Tubes plus Adenoidectomy;
   LTFU = Lost to follow up (children not completing their 2-year follow-up).
2. Exclusions (green box)
   2.1. Overriding Concern: Where consultant or parent was unduly concerned over a child's speech/language, behaviour, otalgia or nose/throat problems, the child could be managed outside TARGET. Such children differed in the expected ways[4] from included children and in total at visits 1 and 2 represent only 9.8% of children with a confirmed condition at Visit 1.
   2.2. Visit 1 and Visit 2 audiometric inclusion criteria were: better ear HL≥20 dB, air-bone gap >10 dB and binaural tympanogram combination of (B, B) or (B, C2).
   2.3. "Other" exclusions include previous VT/ad surgery, outside age limits, not accompanied by parent/guardian, other medical exclusion, significant family language problems, parent refusing to take part in study, child unable/unwilling to do audiometry, administrative problems, family/social reasons and protocol mishaps, particularly early in the trial.
3. Discontinued centres (grey box)
   3 centres were unable to continue recruiting for TARGET. Children from these centres are excluded from the main TARGET outcomes analyses as they were unable to complete follow up when their centres discontinued TARGET work.
4. Children with HL>40 dB (blue boxes).
   Children with binaural average HL > 40 dB on either qualifying visit were given the option of immediate non-randomised listing for surgery, either VTs or VTs+ad, at the consultant's discretion. All 56 children so listed for surgery were followed within TARGET for 2 years. One child included in this group did not *strictly* meet the criteria with binaural average HL=40 dB.
5. Eligible children (pink box)
   A total of 441 children met the eligibility criteria on both qualifying visits. Of these 16 joined the HL>40 dB program. The remaining were offered entry into TARGET and 49 of these refused randomisation.
6. Children allocated a treatment plan and entered for full 2-ear follow-up (purple box)
   The 376 randomised (yellow boxes) and 56 HL>40 dB children (blue boxes) gave 432 children on whom 2-year follow-up data was collected.

7. Children transferring from allocated treatment continued to be followed for 2-years under TARGET.
8. Data for the 74 follow-up cases were imputed to retain 376 randomised and 56 HL>40 dB cases for analyses. Their final treatment is listed as that recorded at their final attended visit.

Appendix S1: Otomicroscopy Coding Form

TARGET	**Otomicroscopy Coding Form**	☐3☐☐☐ **(Office use)**

(You may wish to use hospital labels for patient details) CONFIDENTIAL

Child's name:	
Date of birth:	
Hospital number:	
Address:	

Date:		**Otologist:**		**Instrument used** *(Please circle)*	**Otoscope/Otomicroscope**

		Right			Left		
Middle Ear Fluid	0 / ? / + / TM not seen (9)						
Pars Tensa		A	B	C	A	B	C
Ventilation tube	0-4						
Chalk patch	0 / ? / +						
Tympanosclerotic plaque	0 / ? / +						
Perforation	none (0) / inactive (+) / active (++) / not sure (?)						
Retraction	Sadé 0-4						
Pars Flaccida		Right			Left		
Attic retraction	Tos 0-5						

Comments: **RIGHT TM** **LEFT TM**

Key to coding scheme

Retraction (Sadé)

0: no retraction
1: slight retraction
2: retraction of TM touching incus or stapes
3: TM touching promontorium
4: adhesive otitis media

Ventilation tube

0 N/A
1 functioning
2 extruded
3 blocked
4 infected

Attic retraction (Tos) (See diagrams below)

0: no attic retraction
1: retraction towards neck of malleus, air space visible
2: retraction beyond osseous annulus, bottom of retraction visible when head is tilted; may be slight bone resorption
3: distinct bone resorption of osseous annulus, retraction to head of malleus
4: attic cholesteatoma

Table S1: Mean HL (standard deviation) at baseline and at each visit up to end of 2-year follow-up. Data are presented for (i) maximum number of cases available and (ii) for cases having complete data across all visits. HL data are displayed in Figure 2.

a) HL data

i. Maximum number of cases available at each visit

	FWW		VTs		VTs+ad		Total	
	Mean HL (SD)	N	Mean HL (SD)	N	Mean HL (SD)	N	Mean HL (SD)	N
Baseline (ave visits 1 and 2)	33.8 (4.8)	122	33.2 (4.6)	126	32.8 (5.2)	128	33.2 (4.9)	376
Visit 3 (+3 months)	26.3 (9.9)	106	14.4 (6.9)	109	13.6 (6.0)	116	17.9 (9.6)	331
Visit 4 (+6 months)	23.1 (10.1)	105	17.5 (8.2)	106	15.4 (8.1)	112	18.6 (9.4)	323
Visit 5 (+12 months)	20. 5 (10.1)	100	21.0 (9.4)	110	17.1 (9.1)	111	19.5 (9.7)	321
Visit 6 (+18 months)	19.7 (10.4)	98	21.1 (10.2)	103	15.7 (7.3)	103	18.8 (9.6)	304
Visit 7 (+24 months)	18.2 (8.1)	102	18.7 (8.9)	108	14.8 (7.7)	109	17.2 (8.4)	319

a) HL data

ii. Cases with complete data at all visits

	FWW		VTs		VTs+ad		Total	
	Mean HL (SD)	N	Mean HL (SD)	N	Mean HL (SD)	N	Mean HL (SD)	N
Baseline (ave visits 1 and 2)	34.5 (4.7)	76	33.6 (4.6)	85	32.8 (4.9)	92	33.6 (4.8)	253
Visit 3 (+3 months)	26.3 (10.3)		14.4 (6.8)		13.8 (6.4)		17.8 (9.6)	
Visit 4 (+6 months)	23.9 (10.7)		18.2 (8.7)		15.2 (7.3)		18.8 (9.5)	
Visit 5 (+12 months)	20.4 (9.9)		20.4 (9.1)		16.5 (8.0)		19.0 (9.1)	
Visit 6 (+18 months)	20.3 (10.3)		21.5 (10.3)		15.6 (7.2)		19.0 (9.6)	
Visit 7 (+24 months)	18.3 (8.2)		18.4 (8.6)		14.8 (7.7)		17.1 (8.3)	