Health Technology Assessment 2009; Vol. 13: No. 37

A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care

I Williamson, S Benge, S Barton,
S Petrou, L Letley, N Fasey,
G Abangma, H Dakin and P Little

August 2009
DOI: 10.3310/hta13370

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

How to obtain copies of this and other HTA programme reports
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care

I Williamson,[1*] S Benge,[1] S Barton,[2] S Petrou,[3,4] L Letley,[5] N Fasey,[5] G Abangma,[3] H Dakin[3] and P Little[1]

[1]Primary Medical Care, University of Southampton, Aldermoor Health Centre, Southampton, UK
[2]University of Southampton Clinical Trials Unit, Southampton General Hospital, Southampton, UK
[3]Health Economics Research Centre, University of Oxford, Old Road Campus, Headington, Oxford, UK
[4]National Perinatal Epidemiology Unit, University of Oxford, Old Road Campus, Headington, Oxford, UK
[5]Medical Research Council General Practice Research Framework, London, UK

*Corresponding author

Declared competing interests of authors: none

Published August 2009
DOI: 10.3310/hta13370

This report should be referenced as follows:

Williamson I, Benge S, Barton S, Petrou S, Letley L, Fasey N, *et al.* A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care. *Health Technol Assess* 2009;**13**(37).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/72/02. The contractual start date was in September 2003. The draft report began editorial review in May 2008 and was accepted for publication in February 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.

Abstract

A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care

I Williamson,[1*] S Benge,[1] S Barton,[2] S Petrou,[3,4] L Letley,[5] N Fasey,[5] G Abangma,[3] H Dakin[3] and P Little[1]

[1]Primary Medical Care, University of Southampton, Aldermoor Health Centre, Southampton, UK
[2]University of Southampton Clinical Trials Unit, Southampton General Hospital, Southampton, UK
[3]Health Economics Research Centre, University of Oxford, Old Road Campus, Headington, Oxford, UK
[4]National Perinatal Epidemiology Unit, University of Oxford, Old Road Campus, Headington, Oxford, UK
[5]Medical Research Council General Practice Research Framework, London, UK

*Corresponding author

Objectives: To determine the clinical effectiveness and cost-effectiveness of topical mometasone in children with bilateral otitis media with effusion (OME).
Design: A double-blind randomised placebo-controlled trial with an intention to treat analysis; the 10.6% of patients lost to follow-up at 1 month were censored in the analysis.
Setting: 76 Medical Research Council General Practice Research Framework practices throughout the UK between 2004 and 2007.
Participants: A sample of 217 children aged 4–11 years was selected from those presenting to their GP with one or more episodes of otitis media or ear-related problems in the previous 12 months whom the research nurse confirmed had bilateral glue ear using microtympanometry (B B or B C2 types using a modified Jerger classification) at randomisation.
Interventions: Mometasone 50 μg in each nostril or placebo spray once daily for 3 months.
Main outcome measures: The primary outcome was the proportions of children cleared of OME assessed by tympanometry at 1 month. Secondary outcomes included clearance at 3 months and 9 months; adverse events; OM8-30 scores (a functional health status responsive disease-specific measure); hearing loss; days with otalgia; cost-effectiveness; and health utilities.
Results: Of the topical steroid group, 40.6% (39/96) demonstrated tympanometric clearance (C1 or A type) in one or both ears at 1 month, compared with 44.9% (44/98) of the placebo group. The absolute risk reduction at 1 month was –4.3% (95% CI –18.05% to 9.26%); the odds ratio (OR) was 0.84 (95% CI 0.48 to 1.48). Four covariates were pre-specified for inclusion in logistic regression analysis: age as a continuous variable ($p = 0.94$), season ($p = 0.70$), atopy ($p = 0.61$) and clinical severity ($p = 0.006$). The adjusted OR (AOR) at 1 month for the main outcome was 0.93 (95% CI 0.50 to 1.75). Secondary analysis at 3 months showed 58.1% of the steroid group had resolved and 52.3% of the placebo group, AOR 1.45 (95% CI 0.74 to 2.84). At 9 months 55.6% of the treated group remained clear in at least one ear and 65.3% of the placebo group, AOR 0.82 (95% CI 0.39 to 1.75). Adverse events (although relatively minor) occurred in 7–22% of children and included nasal stinging, epistaxis, dry throat and cough. The OM8-30 scores ($p = 0.55$) reported hearing difficulty ($p = 0.08$), and days with otalgia ($p = 0.46$) were not significantly different between groups at 3 months. The economic evaluation found the active treatment arm to be dominated by placebo, accruing slightly (but not significantly) higher costs and fewer quality-adjusted life-years (QALYs), with a 24.2% probability that topical steroids are a cost-effective use of NHS resources at a ceiling ratio of £20,000 per QALY gained.
Conclusions: Use of topical intranasal corticosteroids is very unlikely to be a clinically effective treatment for OME (glue ear) in the primary care setting.
Trial registration: Current Controlled Trials ISRCTN38988331.

Contents

List of abbreviations

ACET	air conduction estimated from tympanometry (OM8-30 questionnaire)
AM	active monitoring
ANOVA	analysis of variance
AOM	acute otitis media
AOR	adjusted odds ratio
AR	absolute risk
ARI	absolute risk increase
BL	baseline
BNF	*British National Formulary*
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	CONsolidated Standards On Reporting Trials
CUA	cost–utility analysis
daPa	deka Pascal (measure of middle ear pressure)
DEV	developmental score (OM8-30 questionnaire)
DMEC	Data Monitoring and Ethics Committee
ENT	ear, nose and throat
EQ-5D	EuroQoL 5-dimension multi-attribute utility measure (standard 3-level version)
$EQ\text{-}5D_5$	5-level version of the EuroQoL 5-dimension multi-attribute utility measure
GLM	generalised linear model
HI	hearing impairment
HL	hearing level
HUI	health utilities index
ICER	incremental cost-effectiveness ratio
INCS	intranasal corticosteroids
IQR	interquartile range
ITT	intention to treat
MAE	mean absolute error
MEE	middle ear effusion
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MSE	mean squared error
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NRES	National Research Ethics Service (formerly COREC – Central Office for Research Ethics Committees)
NS	not significant
OLS	ordinary least squares
OM8-30	30-question questionnaire on the impact of otitis media
OME	otitis media with effusion
OR	odds ratio
PCT	primary care trust
PHYS	physical health score (OM8-30 questionnaire)
PPV	positive predictive value
PTA	pure tone audiometry
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial

continued

RESP	respiratory symptoms score (adenoidal factor from OM8-30 questionnaire)
RHD	reported hearing difficulties (OM8-30 questionnaire)
RN	research nurse
RR	relative risk
RTN	regional training nurses
SD	standard deviation
SE	standard error
TARGET	trial of alternative regimens in glue ear treatment
TSC	Trial Steering Committee

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Otitis media with effusion (OME), which is often called glue ear, is an increasingly common presentation in primary care and the commonest reason for childhood surgery. A recent National Institute for Health and Clinical Excellence (NICE) review found that there are no proven effective medical treatments. Topical steroids delivered as a nasal spray may be beneficial, are under-researched and may be effective in a primary care setting where the majority of such children are seen.

Objectives

To determine the clinical effectiveness and cost-effectiveness of topical mometasone (a nasal steroid) in children with OME in both ears. The children in this group stand most to gain from a medical intervention because they have more disability than those who have the condition in only one ear, and are also more likely to be referred for surgery.

Methods

Design

A double-blind randomised placebo-controlled trial design was used as this is the best method for evaluating a medical intervention for which previous studies suggest there may be an effect but have been inconclusive. It involves reduction of subjective bias by blinding both observers and subjects and allocating treatments at random rather than through clinician or subject choice.

Setting

Seventy-six Medical Research Council General Practice Research Framework practices throughout the UK between the years 2004 and 2007.

Participants

Two hundred and seventeen children aged 4–11 years. The sample was selected from children presenting to the GP with one or more episodes of otitis media or ear-related problems in the previous 12 months, and whom the research nurse confirmed had glue ear on both sides using microtympanometry (B B or B C2 types using a modified Jerger classification) at entry into the main study. Tympanometry is a painless, quick and reliable method of assessing if the child has fluid behind their eardrums, by using a probe with a pressure seal at the ear canal which measures sound reflected back off the eardrum surface as the pressure is made to change.

Interventions

Mometasone furoate, a topical steroid, 50 µg squirted into each nostril, or placebo spray (a dummy spray that looks and tastes the same), once daily for 3 months.

Primary outcome measure

Proportions of children cleared of glue ear assessed by tympanometry at 1 month.

Secondary outcome measures

Tympanometric clearance at 3 months and 9 months after starting the treatment; adverse events (a retrospective questionnaire-based score developed by the Medical Research Council); the OM8-30 score (a functional health status-responsive disease specific measure); reported hearing difficulty; days with earache recorded in a contemporary 3-month diary; health utilities; resource use and cost; and cost-effectiveness [measured both as the cost per quality-adjusted life-year (QALY) gained and as the cost per tympanometric cure at 1 or 3 months].

Results

For the main outcome at 1 month, 40.6% (39/96) of the topical steroid group demonstrated tympanometric cure (to C1 or A type) in one or both ears, as did 44.9% (44/98) of the placebo group. The absolute risk reduction at 1 month was

calculated at –4.3% [95% confidence interval (CI) –18.05% to 9.26%]; the odds ratio (OR) was 0.84 (95% CI 0.48 to 1.48). In other words, there was no difference in the rate of resolution of children getting better irrespective of being allocated to either the treatment group or the dummy group. The absolute risk reduction in the treated group at 1 month was actually worse than in the placebo group (–4.3%). Based on these data (100/9.26), the study found that at least 11 children would require to be treated for 1 month with nasal steroids for one child to potentially benefit, and, using the average study value, the number needed to treat for one to benefit would actually be much greater than this.

Four factors were pre-specified for inclusion in adjusting the analysis – age, season, allergy and severity of the glue ear – but only illness severity was found to affect the results. Even when an adjusted analysis was carried out, no treatment effects were found at 1, 3 or 9 months after the start of treatment as shown by the fact that the adjusted OR (AOR) at 1 month for the main outcome was 0.93 (95% CI 0.50 to 1.75). At 3 months, 58.1% of the steroid group had resolved compared with 52.3% of the placebo group, AOR 1.45 (95% CI 0.74 to 2.84). At 9 months 55.6% of the treated group remained clear in at least one ear compared with 65.3% of the placebo group, AOR 0.82 (95% CI 0.39 to 1.75).

Side effects of the spray, although relatively minor, occurred in 7–22% of children and included nasal stinging, nosebleeds, dry throat and cough. OM8-30 scores, reported hearing difficulty and days with earache were not significantly different between groups at 3 months.

The active treatment arm of the study was found to accrue slightly (but not significantly) higher costs and fewer QALYs than placebo and was therefore dominated by placebo in the cost–utility analysis. The probability that topical steroids are a cost-effective use of NHS resources at a ceiling ratio of £20,000 per QALY gained was 24.2%. Ceiling ratios comprise possible values for the maximum that society is willing to pay to gain one unit of health benefit (e.g. one QALY or one tympanometric cure), or the minimum that society is willing to accept in exchange for losing one unit of health benefit. A secondary economic evaluation used a composite end point whereby a patient was considered cured if they had resolution of OME at either 1 or 3 months after start of treatment; this end point differs from the primary and secondary end points of the trial. As slightly more patients randomised to active treatment achieved tympanometric cure at either 1 or 3 months after start of treatment, topical steroids cost £347 per additional child cured, but had only a 56.4% probability of being cost-effective at a ceiling ratio of £1000 per child cured.

Conclusions

Use of topical intranasal corticosteroids (steroid nasal spray) is very unlikely to be clinically effective for glue ear in the primary care setting.

Implications for health care

Topical nasal steroids are not an effective or worthwhile treatment for glue ear in primary care (or likely to be in secondary care because our sample was as badly affected as a large British secondary care sample).

Active monitoring in primary care for children with suspected glue ear is acceptable and satisfactory to children and families, but the current technology methods used to monitor children may require adaptation.

Relatively few children with histories of ear problems attending the GP surgery have glue ear actually confirmed on both sides and need treatment.

Active monitoring in primary care appears to have high satisfaction and low referral rates, but may be in part due to effects of a dummy medication while natural resolution is observed.

Recommendations for research

Seek alternative treatments feasible in this setting, and an evidence review (NICE 2008) suggests that first among these would be auto-inflation. A non-blinded randomised controlled trial would be required with objective outcomes such as tympanometry, and could also be used to look more specifically at accurate diagnostic methods for glue ear in this setting. (Because the condition is highly recurrent after resolving, this favours low-cost, low-side effect-type interventions in primary care.)

In the absence of a proven treatment there is a need for good information to be developed for children, parents and guardians to support active monitoring in primary care.

Steroids may have a place in treating targeted children in secondary care. However, they are unacceptable when given orally (because of potentially severe side effects), and are very likely to be ineffective when given topically. Future studies that look at older children or those who have more marked allergies may define subgroups that benefit.

Trial registration

This trial is registered as ISRCTN38988331.

Chapter 1
Introduction

Glue ear is an increasingly common presentation in primary care and the commonest reason for childhood surgery. There are presently no proven effective medical treatments, but topical intranasal steroids may be beneficial and are under-researched.

Definition

The condition of otitis media with effusion (OME) is characterised by fluid secretion or effusion behind the eardrum, without any signs of acute inflammation, and often develops insidiously after a typical acute ear infection appears to have settled. Such 'sterile' fluid in the middle ear may act as a mechanical damper to the transmission of sound energy to the inner ear by restricting the eardrum vibration movements, and so produce deafness from impaired air conduction. Fluid in the middle ear can also progress in some children into a chronic remitting and relapsing condition widely known as glue ear (when effusions have persisted for at least 6 weeks and become more mucoid or glue-like), but with the terms OME and glue ear often used interchangeably or synonymously in clinical practice. The more chronic state of persistent effusion can lead to significant hearing losses (hence severity), especially when both ears are affected. Furthermore, such temporal losses are often noted at important times in the child's development.

Background

OME is a very common cause of morbidity and related disability in children and of costs to the NHS. Estimated costs for all types of otitis media management in primary care are about £200M per year, of which about 10–30% could be attributed to OME cases[1] and is mostly due to inappropriate antibiotic prescribing because the number needed to treat (NNT) is approximately 1 in 20.[2] Surgical costs for grommets, the operation used to treat glue ear, are estimated at about £30M annually, making a total estimated combined cost to the NHS of about £50M–90M per year.[3,4] The majority of children are referred from primary care usually with concerns about development or physical health,[5] but confusions over effective treatment and uncertain diagnosis[2,6] have historically contributed to a broad and at times inequitable gateway to secondary services. Publication of the effective health-care bulletin questioning the evidence base for surgery in the early 1990s appeared initially to curb the processes of referral.[7] There has been a slow decline in grommet rates over the past decade, while OME labelling appears to have increased in frequency in primary care.[1,8] The present National Institute for Health and Clinical Excellence (NICE) 2008 review suggests that grommets are cost-effective, particularly in older children.[4] Thus, the requirement to develop less invasive and costly forms of effective treatments suitable for primary care delivery is an urgent priority.

OME medical treatments are reviewed separately in Cochrane: steroids,[9] grommets,[10] decongestants and antihistamines,[11] with antibiotics reviewed in a meta-analysis by Cantekin.[12] All non-surgical treatments are reviewed by NICE[4] and *BMJ Clinical Evidence*.[2] The summary of these data indicates that there are no proven effective medical interventions, whereas surgery is cost-effective, particularly for those children most severely affected. This leaves a majority of children at an earlier stage of the natural history than secondary care cases with moderate OME, and the need for a less invasive treatment option feasible for primary care delivery in which the majority of children are seen and managed. OME leads to variable and intermittent hearing loss and delays in language and behaviour development, and remains the most common reason for surgery in children.[13–15] While the trial of alternative regimens in glue ear treatment (TARGET) is currently clarifying the role for surgery in restricted and persistent cases, there is therefore (and likely to remain) a need for medical treatments for useful temporising management that either aid natural resolution or could be used prior to or as an alternative to surgical management.[16,17]

The aims of all interventions should be to secure timely improvement in the hearing and well-being of affected children and to minimise poor behavioural, speech and educational outcomes.[13]

Thus it is important to carry out a study analysis with children as the unit rather than individual ears (which are also not independent).[9] OME is known to be a highly recurrent condition with a mean duration of 6–10 weeks,[18] so outcomes also need to be evaluated over a reasonable 6-month to 1-year period, particularly when evaluating cost-effectiveness outcomes for the NHS. This is because natural history effects and timing variations in the approximate management sequence, observation/medical treatment/referral/audiology/surgical treatment,[4,18–20] act over such prolonged timescales. Few quality studies of any treatment have, however, followed up children beyond 3 months, and very few address more child-centred outcomes and quality of life (QoL) issues.[2,21] An extensively used psychometric approach has been taken by the Medical Research Council (MRC) to identify the core areas of impact on children using a sensitive and responsive functional health measure specifically designed for children with OME (the OM8-30), and provides an appropriate method of evaluating the effectiveness of interventions for OME (M Haggard, MRC Cambridge, June 2006, personal communication).[14] The use of a validated QoL measure is essential in addition to more objective measures of tympanometry and audiometry, as there is only an approximate correlation between the observed outcomes of tympanometry, hearing thresholds and the reported QoL.

Impact of otitis media with effusion on children over time

Epidemiological studies of OME reveal that it affects 50–80% of children by the age of 5 years,[20,22] with 2 per 1000 (the most severely affected children) receiving surgery per year.[3,8] These and other data confirm the magnitude of the problem of OME on child health as being of the first order, although total impact remains difficult to quantify precisely. This is because the very high cumulative prevalence of effusions in the general child population makes the finding of effusion-free control children necessarily difficult with no good prospective control cohort studies available.[5,23] The diverse natural history of such middle ear effusions is observed both as wide variation in the duration or persistence of the effusion, and also in a somewhat unpredictable relationship between actual presence of an effusion behind the ear(s) and the associated severity of any disability a child may encounter.[13,14] In particular, bilateral OME is more significant as a cause of disability than a unilateral loss. OME causes not just hearing losses in children but also short-term functional disabilities, particularly in noisy environments such as school, playgroup and other learning environments.[24] But the full impact of the condition on development, and long-term development in particular, is only partially understood. The view that longer term benefit from ventilation tubes (the only established effective intervention) on development is marginal or negligible is supported by Cochrane.[10] Very long-term effects of the condition remain unknown. The Paradise trial follow-up on 9- to 11-year-olds concluded that there were no demonstrable long-term disabilities in their selected sample,[25] whereas an earlier paper by Bennett *et al*.[15] reported that some developmental effects persist into teenage years, particularly on reading ability. In the main, however, these study data support the importance of potential child benefit for interventions aimed principally at short- to medium-term outcomes for evaluation in clinical trials.

Children with poor speech, language comprehension and writing skills may arguably stand to gain most from a developmental perspective, and improved targeting of these children may prevent reading problems developing, but the effect of such targeting has not yet been proven. The work of Moore *et al.*[26] has identified the effects of ear canal blockage in young rats, and found reduced contra-lateral auditory neural connections to the blocked ear side. Assuming a critical period for development hypothesis, it is reasonable to suppose that not only children but even young adults with histories of OME may be disadvantaged in some situations because such suboptimal 'wiring' is unequal to the task later encountered. The extent to which retraining effects occur is a moot point, and Cochrane comments that maternal education level, gender, socioeconomic group and quality of care seem able to offset the effects due to time with effusions.[10] There is thus evidence to suggest that improving communication styles and improved coping strategies for children and families during the watchful waiting or active monitoring (AM) period would be a worthwhile adjunct to treatment in both primary and secondary care populations.[4] The term AM is preferred to the more passive *watchful waiting*, in line with the NICE review[4] to emphasise the structured nature of the support and measurements and, specifically, to the time before giving the intervention in this study.

Diagnosis and management

Children usually present by proxy parental concerns that relate to physical ill health, recurrent ear infections or associated problems, poor hearing, speech, reading, language skills, educational underachievement and poor behavioural development.[27] Such presentations to the NHS meet with a variety of health managements along with 'watchful waiting' observations, which often include unsubstantiated use of either ineffective or untested non-surgical treatments in primary care as temporising management before either ear, nose and throat (ENT) or audiology referral, with surgical intervention for the most severe cases. This overuse of medical treatment in primary care has been questioned by NICE.[4]

Current diagnostic assessments readily available to the GP lack precision because of the fairly poor predictive values of the techniques currently used, such as the history and simple otoscopy.[4,6,28] The between GP variation in referral for grommet consideration is five times higher than for referral for assessment for tonsillectomy in recurrent tonsillitis cases, and comparative lack of diagnostic precision for OME and structured assessments may contribute to this.[29] Generally the specificity of the carer history is good but it is not sufficiently sensitive (cases may be missed).[30] The positive predictive values (PPVs) for methods currently employed by practices in the main remain low. Relatively few practices (probably less than 5%) have audiometers and/or tympanometers on their premises to aid more accurate diagnosis and improve the PPV of referral (by excluding non-cases),[31] although it has been speculated that indiscriminate use of tympanometry in primary care could lead to over referral.[32]

Selection of appropriate children for referral and treatment remains a clinical priority but simple markers of severity and persistence such as season, day care, frequency of episodes (infection load) and maternal smoking could be better established and used in this setting.[13,33–36]

Referral for early surgical intervention to prevent disability developing has been part of the underlying philosophy of treatment, but current interpretation of the existing evidence is challenging this because of the clinical heterogeneity in surgical trials in Cochrane with potential for differential treatment effects.[10] The trials in Cochrane excluded many of the cases of 'syndrome' children who usually receive grommets, and also those with speech, language and behavioural problems. Grommets may not be so effective in some of the included study populations because they had been put in too early, and for too mild a disease. This, however, is much less likely the case in the UK where a quite conservative approach to grommets is practised, usually in older children, with their cost-effectiveness established for these more severely affected children. Thus an initial repeated measures or AM approach for 3–6 months appears currently very well justified, and has support from a recent individual patient data meta-analysis.[33] The best setting for such monitoring is determined in part by feasibility and costs, best informed by measured or reported severity, and may be proportioned between primary and secondary care by discriminate use of the gate-keeper role that aims to target appropriate children and prevent over referral.

Audiology services have an important role to play in all AM of children in the community, and provide expert age-related assessments. However, these services are of restricted provision. Hearing aids are an option some children may prefer, but they are unlikely to provide a viable option to surgery for the majority of affected children.

In summary, there is a case for improved efficiency of management in primary care through better risk assessments that includes recognition of true cases and true negatives using improved or more objective diagnostic assessments with routine timely use of AM for 3 months before targeted referral of needy children. While the majority of non-surgical treatments in primary care have been categorically advised against by NICE, only auto-inflation and hearing aid options have been recommended as current viable options, with the role of topical steroids requiring more evidence.[4] No existing option has conclusive evidence to support its use in a primary care setting in which most cases of recurrent ear problems and related developmental concerns are seen, and which could be used judiciously for those children on that wide but narrowing avenue importantly identified as 'suspected OME or glue ear'.

Secondary research on non-surgical interventions

Many non-surgical treatments are used in the NHS as temporising treatments for children with glue ear, in an attempt to buy time and

avoid unnecessary referral and costly surgery. However, there is little current evidence of clear benefit for all of these non-surgical options.[2,4] The purpose of a literature review is to review all such interventions, but for brevity this section will focus only on those interventions more widely used, and on topical steroids in particular, having some preliminary evidence of benefit.

Antibiotics

Re-evaluation of the benefits of antibiotics in OME has shown smaller effect sizes than previously reported by systematic reviews that included poor-quality non-placebo controlled trials (unpublished *BMJ Clinical Evidence*: last search date, and critical appraisal, March 2007).[2] One systematic review based on eight randomised controlled trials (RCTs) of antibiotics versus placebo included 1292 children. No significant difference in cure rate was found: 179/813 (22%) receiving antibiotics and 85/479 (18%) receiving placebo; absolute risk increase (ARI) of cure 4.3% [95% confidence interval (CI) –0.1% to 8.6%], NNT 23.[12] Prescribing antibiotics encourages belief in them, re-attendance and increasing antibiotic resistance in strains of *Streptococcus pneumoniae*.[37–42] Antibiotic resistance, medicalising effects, side effects, costs and substantial compliance issues for longer than three or four times a day courses over at least 10 days (and likely to be repeated) renders them now untenable as a treatment for OME. Furthermore, growing concerns about inappropriate use of antibiotics in the community over the past decade have further sharpened the issues for primary care management of children with OME, for which, because of ongoing demand, there is a perceived need to respond positively with some form of treatment. It appears plausible that antibiotics are increasingly misused in this way for OME.[1] (However, it may also be that in general practice recurrent acute otitis media and OME are only loosely labelled in records and hence confused, thus requiring better differentiation.) Antibiotics are not recommended in the recent NICE guideline, so with persistent demand this is likely to lead to displacement prescribing to other ineffective treatments.[4]

Decongestants and antihistamines

A systematic review found no difference between antihistamines plus decongestants versus placebo at 4 weeks.[43] However, a considerable number of harms were noted including hyperactivity, insomnia, drowsiness, behavioural change, blood pressure variability and seizures; NNT to harm = 9.

Auto-inflation

Two systematic reviews found limited evidence that auto-inflation improved clearance of effusions compared with no treatment from 2 weeks to 3 months. The earlier review found that children using a purpose-manufactured balloon were more likely than untreated control subjects to gain clearance of effusions: absolute risk (AR) 63/195 (32%) with auto-inflation versus 27/191 (14%) with control [odds ratio (OR) 3.53, 95% CI 2.03 to 6.14].[44] A second more rigorous review (although the devices were classified differently between reviews) found no benefit before 1 month in 423 patients from four RCTs, relative risk (RR) 2.47, 95% CI 0.93 to 6.58.[45]

Difficulties arise for younger children attempting to inflate their Eustachian tubes through the required manoeuvre which also needs to be performed fairly regularly throughout the day to achieve optimal results. This severely limits its use in preschool children in particular, which is the main cohort of children suffering with the condition. However, no serious harms are associated with this approach. Older school-age children may gain benefit from this treatment, particularly when a purpose (mass) manufactured device is chosen. One such device (ear-popper), however, is particularly expensive for a condition with high natural resolution rates.

Oral steroids

The use of *systemic* steroids has been recommended in combination with antibiotics as being cost-effective in OME, but this is based on a low-quality meta-analysis, which included trials rejected by the Cochrane review.[9,46] Oral steroids to be taken repeatedly for a common but non-life-threatening condition would raise legitimate concerns over the side effects, particularly on children's growth or severe idiosyncratic reactions.[47] These concerns, in the absence of better evidence of sustained and worthwhile effect from the small and heterogeneous trials included in Cochrane, effectively preclude the use of these steroids for a mild condition with an episodic natural history such as OME.[48–55] There are several theoretical bases for corticosteroid treatment, and these include (1) a direct anti-inflammatory action on the middle ear and Eustachian tube by reducing arachidonic acid concentration, thereby inhibiting the cyclo-oxygenase and lipo-oxygenase synthetic pathways for pro-inflammatory mediators; (2) an increase in Eustachian tube surfactant, improving tubal function; (3) shrinkage of peritubal lymphoid tissue or encroaching adenoidal tissue, thus improving tubal function; and (4)

reducing middle ear viscosity through an effect on mucoproteins.[9,56–59]

Topical intranasal corticosteroids

Of the theoretical reasons given above, only the third would be anticipated to be a direct benefit from topical steroids, although anti-inflammatory anti-atopic decongestant effects on the nasal mucosa may cause secondary benefits to middle ear drainage and function, for example in a manner analogous to the beneficial effects of topical nasal steroids improving resolution in acute and chronic rhino sinusitis. Thus, on a priori grounds, *topical* intranasal steroids are a logical treatment for evaluation in OME in children, and are more acceptable with fewer harms than oral corticosteroids that might need to be taken over several months.

Indeed, for these and other reasons, topical intranasal corticosteroids (INCS) are already widely prescribed off licence in ENT departments and to some degree in primary care.

Therapeutic use of topical intranasal steroids in OME has now been identified to be of potential value by the Cochrane review (date of last search January 2002). The review, however, does not actually recommend use of topical nasal steroids, because of insufficient high-quality evidence, although the favourable trial by Tracy and Demain[60] was highly rated on methodological criteria. This trial included only 61 children, and was set in a military airbase in the USA, limiting generalisability to a UK general population. Although the paper evaluated short- and intermediate-term efficacy, it did not address the appropriate longer term cost-effectiveness via the broader outcomes necessary for a comprehensive evaluation of this frequently and very variably managed childhood condition. However, this preliminary evidence, if shown to be repeatable in UK general practice, might prove to be highly efficient in reducing referrals by effectively buying many children in the system a disease/disability-free year. This could be maximised by synchronising the critical management decisions and timing of treatment with the major natural seasonal phase of resolution (from winter to summer).Thus any treatment should be aimed at the winter months (the time of maximal incidence) and, due to the relatively slow resolution of OME, should preferably be given for several months. There are some unpublished data in a small cohort of children followed up to age over 4 years (G Scadding, Royal National Throat, Nose and Ear Hospital, 2002, personal communication) with a related publication: a double-blind RCT of Flixonase® in children aged under 4 years from a tertiary care setting in the UK.[61] This very small trial has good adherence over 2 years' follow-up and appears observationally effective in preventing recurrences of OME in a severe case-mix group.[61] An older, low-quality study showed no benefits of topical steroids,[62] but a more recent small RCT from Turkey has shown benefit from topical steroids in clearing effusions.[63] Serious side effects for inhaled topical steroids are rare, but there are concerns that, as with asthma treatments, growth may be affected.[64,65] This makes it imperative that a topical steroid is used with minimal systemic effects.[65–68]

No RCTs from a UK primary care population have been previously performed or published, hence treatment effects are unknown in the main setting in which children present, and thus there is no evidence base to guide the optimal management of the bulk of significant but generally milder cases than seen in hospitals (differences of case-mix limits generalisability to primary care, from published secondary care trials). Any trial on cost-effectiveness needs to consider which groups are most likely to benefit. Thus the current study aims to define what might be feasible and adequate cost-effective temporising management in primary care, by focusing on children with bilateral disease in whom disability is worse and where natural resolution has not occurred quickly, i.e. after tympanometric confirmation, and in the group most likely to be referred, i.e. 4 years and older. Medical treatment in these groups is most likely to impact on NHS resource use. To increase the robustness and stringency of the trial, microtympanometry was used. There is a need to evaluate improved systems of AM and treatment for affected children and their families at a time when demand for surgery could rise again when the TARGET findings are published with some policy expectations for the NHS (changing patterns of NHS use, and an overall increase in referral?).[4] Thus an NHS trial not only should document referral rates in long-term follow-up, but also needs to assess the potential impact of different referral rates and thresholds on secondary management. A well-delivered and well-timed course of nasal steroids has the potential to reduce ineffective prescribing and referral of children for consideration of surgery and so be cost-effective for the NHS. But because it is unclear about the efficacy of nasal steroids as a treatment for OME, the case for their efficacy has to be established first.

In summary, a review of the evidence made it clear that there was a need for a trial of topical nasal steroids in OME with the following features:

- children with previous or recurrent otitis media confirmed as bilateral effusions (OME) on tympanometry
- includes follow-up in the medium to longer term (9 months)
- addresses validated child-centred outcomes (e.g. QoL issues) in addition to audiometry and tympanometry
- uses a topical steroid treatment with low systemic absorption for at least 3 months (during the winter months)
- assesses benefit in those children who are most likely to be referred (i.e. 4 years and older)
- assesses health service resource use and models the impact of potential changes in referral pattern.

Chapter 2
Methods

Introduction

Aims

- To test the clinical effectiveness and cost-effectiveness of topical intranasal steroids over 1 year in a pragmatic clinical trial based in primary care.
- To build a health economic model of total health-care utilisation costs for an affected cohort, were such an intervention to be applied to identifiable children at feasible stages in the health-care system.

Design

The study was designed as a double-blind randomised placebo-controlled trial conducted and reported in accordance with the CONsolidated Standards On Reporting Trials (CONSORT) guidelines. In order to obtain level 1 evidence relating to both efficacy and effectiveness of topical INCS (see Evidence for topical intranasal corticosteroids).

Setting and ethics committee approval

General practices that were part of the MRC's General Practice Research Framework were approached by the MRC and invited to take part. Practices invited were from a range of locations and included small, medium and large practices as well as Carstairs deprivation scores to ensure a representative final sample. All of the practices that took part had a research nurse (RN) attached to them and a lead GP acting as principal investigator. Multicentre ethical approval was granted by the Metropolitan Multi-centre Research Ethics Committee. As the study had local investigator status, site-specific ethical favourable opinions were sought and obtained from all the relevant local ethics committees (*Table 1*). All related Primary Care Trusts (R&D offices) were approached and approvals were obtained (*Table 1*).

Recruitment and training of research nurses

The study intended to commence with 60 practices, (i.e. 60 RNs). This figure was to be kept constant throughout the 4 years, with replacement RNs/practices recruited for those that withdrew. Each practice was to recruit seven eligible randomised children over three winters. All RNs were employed by their practices and were reimbursed for their time working on the study. Some conducted the study in their contracted hours if they held other positions within the practice, others who were employed by the practice only to conduct research studies managed their own time accordingly. The Department of Health awarded service support costs for the RNs' time on the study.

Training

All RNs attended a training day held centrally in London and conducted by the chief investigator, the study manager, MRC senior nursing staff and regional training nurses (RTNs). In-depth training was given on all aspects of the study, including finding potential participants, providing information, taking consent, data protection, the different assessments and procedures. A study handbook provided detailed instructions on all aspects of the study protocol for each RN. The RNs received detailed training on how to use the study equipment (MTP–10 tympanometer) from a representative of the supplying company (Starkey Laboratories). The central co-ordinating team also learnt the techniques in order to troubleshoot any queries the RNs had once they got started. The Starkey representatives also offered their services throughout the entire study for more technical and mechanical queries. Information regarding the nasal spray was supplied by the company (Schering-Plough) and training was also given for the appropriate method of using the spray with the chin up so that the maximal dose to the posterior nasal space was achieved. Quality control visits were performed by the RTNs. They visited each RN three times: (1) to observe consent, (2) to observe

TABLE 1 *Local research ethics committees (LRECs) and Primary Care Trusts (PCT; R&D offices) covering the study*

LREC	PCT[a]	Number of practices
Airedale	Craven, Harrogate and Rural	1
Barnet, Enfield and Haringey	Barnet	1
Barnet, Enfield and Haringey	Haringey Teaching	1
Barnsley	Barnsley	1
Bath	Mendip	1
Bath	West Wiltshire	1
Bolton	Bolton	2
Bolton	West Lancashire	1
Borders	Borders Health Board	1
Bradford	North Bradford	2
Central and South Bristol	Bristol North PCT	1
Cornwall	North and East Cornwall	1
Cornwall	Exeter	1
Dyfed Powys	Pembrokeshire Local Health Board	2
Dyfed Powys	Powys Local Health Board	1
East Berkshire	Bracknell Forest	1
East Dorset	Poole	1
East Kent	Medway	1
East Lancashire	Burnley, Pendle and Rossendale	1
East Somerset	Mendip PCT	1
East Suffolk	Waveney	1
East Surrey	East Elmbridge and Mid Surrey	2
Fife	Fife	3
Forth Valley	Forth Valley	1
Gloucestershire	Cotswold and Vale	1
Grampian	Grampian Local Health Board	1
Greater Glasgow	Greater Glasgow	1
Herefordshire	Herefordshire	2
Hertfordshire	Royston, Buntingford and Bishop's Stortford	1
Highland	Highland Health Board	1
Maidstone and Tunbridge Wells	South West Kent	1
Medway and Dartford	Medway	2
Mid and South Buckinghamshire	Vale of Aylesbury	1
Morecambe	Morecambe Bay	1
North and East Devon	East Devon (Exeter)	1
North and East Devon	North Devon	3
North and East Devon	Exeter	2
North and Mid Hampshire	North Hampshire	2
North Cumbria	West Cumbria	1
North Tees	Durham Dales	1

TABLE 1 *Local research ethics committees (LRECs) and Primary Care Trusts (PCT; R&D offices) covering the study (continued)*

LREC	PCT[a]	Number of practices
North-west Surrey	Woking	1
North-west Surrey	Guildford and Waverley	1
Northampton	Northampton	1
Northampton and Kettering	Northamptonshire Heartlands	1
Norwich	Broadland	1
Nottingham City Hospital	Broxtowe and Hucknall	1
Oldham	Heywood and Middleton	1
Oxford	South West Oxfordshire	1
Oxford	South East Oxfordshire	1
Peterborough and Fenland	South Peterborough	1
Plymouth	Exeter	1
Portsmouth and South-east Hampshire	East Hampshire	1
Queens University Belfast		4
Scarborough and North-east Yorkshire	Scarborough, Whitby and Ryedale	1
Shropshire	Shropshire County PCT	1
Solihull	Solihull (South Birmingham)	1
South Cheshire	Warrington	1
South-east Wales	Cardiff	1
South Tees	Langbaurgh	1
South Tees	Durham and Dales	2
South Tees	Middlesbrough	1
Southampton and South-west Hampshire	Eastleigh and Test Valley South	1
Surrey Borders	Richmond and Twickenham	1
Tayside Committee on Medical Research Ethics	NHS Tayside	1
United Bristol Healthcare Trust	Bristol North	1
United Bristol Healthcare Trust	North Somerset	1
Walsall	Walsall	2
Walsall	Walsall Teaching	1
West Berkshire	Windsor, Ascot and Maidenhead	3
West Suffolk	Ipswich	1
West Sussex	Adur, Arun and Worthing	1
Worcestershire	Redditch and Bromsgrove	2
Worcestershire	Herefordshire	1
Worcestershire	South Worcestershire	2
Worcestershire	Wyre Forest	2
York	Selby and York PCT	1
West Cumbria	Carlisle and District	1

a Due to NHS trust restructuring, some of these trusts may have merged or changed their names.

the RN completing the baseline measures and (3) on a follow-up visit. The RNs were monitored to check adherence to the study protocol and ICH-GCP. The RTNs also provided support to the RNs whenever required.

Recruitment of children

The study employed two approaches to identify potential participants. Firstly, suspicion of a diagnosis of OME in 4- to 11-year-old children by a GP, health visitor or nurse. These people would refer suspected new cases to the RN for confirmation of the diagnosis. The second approach was a structured audit for which 'at risk' children were invited to be screened. This latter approach was performed using read codes to carry out practice computer searches. The read codes covered OME, typical OME histories (i.e. hearing loss, snoring, behaviour concerns, speech concerns, educational concerns) and acute otitis media (AOM). The searches were performed on children aged between 4 and 11 years over the 12 months prior to the search date. A child found from these searches was eligible to be invited for screening (to assess further suitability) once the local GP had agreed they could be approached (*Figure 1*). All parents of potentially eligible children found via either referral or the audit were given or sent a patient information sheet outlining all the details of the study. In addition, children aged 6–11 years old were supplied with their own information sheet.

Eligibility and consent

The study population was children aged 4–11 years attending recruiting practices in the previous year with at least one prior episode of an ear-related problem and failing tympanometric screening in both ears on two occasions 3 months apart. Children younger than 4 years were deemed to be unlikely to take a nasal spray reliably, and the natural history and a uniform dosing schedule determined the upper age cut-off point.

Ear-related problems were defined in the study audit protocol and included children attending the GP with any middle-ear disease-related episode including previous OME, AOM or related concerns such as over-hearing or speech. Children and families agreeing to diagnostic screening by tympanometry to confirm bilateral glue ear were invited for an appointment with the RN. After referral from a health-care professional in the practice or through identification from the audit and subsequent acceptance of an invitation to attend for screening, parents (guardians) brought their children into the practice to be assessed (see *Figure 1* for a child's flow through the study). Parents (guardians) and, when appropriate, the child were given another patient information sheet for them to read. The RN explained the study procedures, answered any questions and checked the exclusion criteria (see initial appointment form, Appendix 2). The parents (guardians) were then asked to give written informed consent. The RN then carried out the first tympanometric screening to assess eligibility for proceeding into the study. Children who failed tympanometry in both ears (i.e. confirmed bilateral OME B/B or B/C2; see *Table 2*) were eligible to proceed into a 3-month period of AM, at the end of which their ears were tested again. Pure tone audiometry was not included as an entry criterion because of poor validity in younger children in this setting, and HL (level of hearing threshold) is not known to be an effect modifier.

Inclusion criteria

- Children aged 4–11 years.
- Attendance at the GP surgery with at least one episode of a related ear problem in the previous 12 months.
- Failing tympanometry, i.e. confirmed bilateral OME (B/B or B/C2) tympanograms on two occasions 3 months apart.

Exclusion criteria

- Children at high risk of recurrent disease for whom early referral is indicated.
- Children with cleft palate, Down syndrome, primary ciliary dyskinesia, Kartagener's syndrome and immunodeficiency states.
- Children with grommets already in place, or referred or listed for grommets.
- Children who have taken systemic steroids in the previous 3 months or have poorly controlled asthma.
- Where there are developmental concerns about the child's growth, frequent or recent heavy epistaxis or known hypersensitivity to mometasone.

Withdrawals

Children were withdrawn according to ethical practice and where any serious adverse event occurred or serious reaction was suspected.

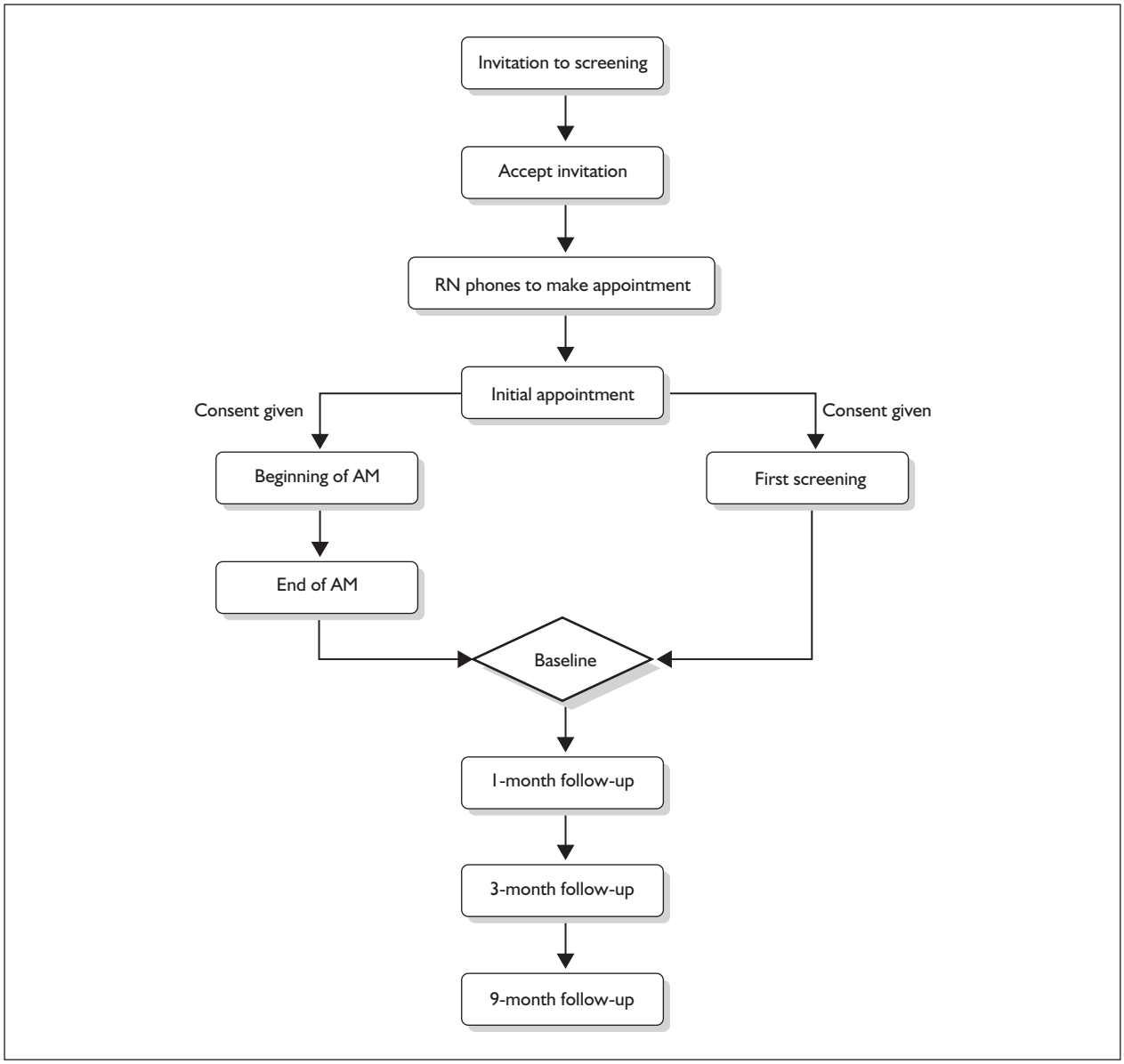

FIGURE 1 *Flow of children through the study (after the initial appointment children originally followed the left-hand path showing AM as per the original protocol; however, during the study AM was removed and so children followed the right-hand path through the study – see Changes to the original protocol for a more detailed explanation).*

TABLE 2 *Tympanometric classification (based on a modified Jerger's classification)*[69,70]

Tympanogram		Middle ear pressure (daPa)	PPV of OME
All have peaks	Type A	+200 to –100	Accepted as normal
	Type C1	from –100 to –199	
	Type C2	–200 to –399	54%
NO peak flat trace	Type B	≤–400	88%

Randomisation and concealment

To ensure blinding was total and complete the study separated all executors from the generator. The supplier, Schering-Plough, used a computer-generated random number sequence to randomise the intervention and placebo into blocks of four. Each block of four contained two active and two placebo codes in random sequence. Labelling and use of identical appearance containers, instructions and nasal sprays (also identical smell/taste) were all provided by Schering-Plough according to these codes and were in numbered auditable sequence. Supplies were forwarded from Schering-Plough directly to participating practices in accordance with practice requests for replenishments. Code break envelopes were available through a 24-hour emergency contact number at Schering-Plough, and practices received code break envelopes only for their sprays. RNs assigned children in blinded numbered sequence, and children were similarly unaware of assignment. The success of blinding was evaluated by asking children and parents (guardians) which treatment they thought they had been allocated to. The randomisation code was not broken at any point (the integrity of the returned code break envelopes from practices was found satisfactory). The study remained completely blinded until the analysis phase.

There was an interruption in the supply of trial sprays from June 2005 to February 2006 due to issues with the placebo spray production. Recruitment was halted over this time, but the 9-month follow-up assessments still took place.

Primary outcome measure

The primary outcome measure was an objective assessment of any treatment effect on resolution at 1 month using tympanometric criteria. This is based on a previous study of topical steroids showing effects at 1 and 3 months and is comparable with other short-term outcomes used for this condition. At 1 month, compliance would be expected to be better and would be less influenced by natural cure and relapse than at 3 months. Resolution or cure of bilateral glue ear (B/B or B/C2 tympanograms) was defined by children with residual unilateral OME only (B/A or C1 or C2/A or C1) at 1 month or complete bilateral clearance (A/C1 or A or C1/A or C1) at 1 month. Because of Cochrane recommendations[9] and unilateral OME having little attendant risk of disability, cure was best defined by children not individual ears. The likelihood for effusion for each tympanogram type is shown in *Table 2*.[71] The RNs all received practical training in tympanometry and received a tympanometry handbook on the training days and refresher training days. Ongoing learning was encouraged through use of the company supplier's training support. The tympanograms were also printed off using the facility on the tympanometer and faxed through to the co-ordinating centre (University of Southampton) for immediate help and support with interpretation. Where necessary, repeat readings were then taken. The tympanometer machines were all calibrated for use prior to starting and annually thereafter.

Frequency of follow-up

The follow-up for the main outcomes was short term at 1 month, medium term at 3 months and long term at 9 months. The 1-month primary outcome was chosen for efficacy, but effectiveness outcomes were also important in the medium to long term. The natural history of OME (6–10 weeks mean duration per episode, ~50% relapse rate),[18] has resulted in outcome measures structured for 3-month timescales, e.g. the OM8-30. This intermediate time frame was also significant clinically as the minimum recommended time for AM, and so important in relation to predictors of resolution.

Assessments

As mentioned above, children were assessed at baseline and at 1 month, 3 months and 9 months post baseline. All children and their parents (guardians) attended their usual GP practice for their assessments. At all assessments the RN completed an audiometry sweep at 25 dB pass/fail over five frequencies: 0.5, 1, 2, 3 and 4 kHz. At the 1-, 3- and 9-month assessments the RNs also performed tympanometry to record bilateral, unilateral or no OME present.

OM8-30

The OM8-30 is a short form assessment for OME that is divided into nine domains: (A) Global Health; (B) Respiratory Symptoms; (C) Ear Problems; (D) Reported Hearing Difficulties; (E) Behaviour; (F) Speech and Language; (G) Sleep Patterns; (H) School Prospects; and (I) Parent Quality of Life (Appendix 6). It produces valid

and reliable measures of outcome (scores) for each of these domains (*Table 3* gives details). The OM8-30 is a standardised efficient assessment tool, defining cases as to health and development status not just pathology, and can also provide data acting as clinical indicators for treatment decisions. The OM8-30 refers to the 3 months prior to its completion and was completed by the parent (guardian) at baseline and the 3- and 9-month follow-up assessments.

Patient symptoms (diary)

Each parent (guardian) was supplied with a diary at baseline that covered 4 weeks before his or her next assessment in 1 month's time and then a second diary for 8 weeks up until the 3-month assessment. The diaries were weekly and asked the parent (guardian) to rate how problematic seven symptoms were each week (0 = not present at all, 6 = as bad as it could be) and also the duration of three other symptoms over the week (see Appendix 10 for a sample week page from the diaries).

Impact on child's life

This was mainly measured using the Costs to Parents form and was to be completed at baseline (Appendix 6), and at the 9-month follow-up by the parent (guardian, Appendix 9). This form also contained additional questions relating to the occupation of the parents to determine their socioeconomic grouping and whether their child suffered from asthma, eczema or hay fever. The diaries that were kept from baseline to the 3-month follow-up also measured impact on the child's life, e.g. disturbed sleep and days off school/playgroup (see Appendix 10 for a sample week page from the diaries).

Adherence and compliance

Seven days after receiving the nasal sprays, both at baseline and at 1 month post baseline, the RN telephoned the parents (guardians) to ask questions about their children's adherence and compliance with the spray using a semi-structured interview by going through the adherence forms (Appendices 6 and 7). The parents (guardians) were also asked what spray they believed their child was taking, i.e. active, placebo or unsure. Adherence was also recorded at the 1- and 3-month assessments by the RN asking the parents (guardians) how often their child had taken the medication (Appendices 7 and 8). Spray compliance was also measured more objectively by weighing the used spray bottles at the co-ordinating centre and recording how much spray was used from baseline to the 1-month assessment (spray 1) and between the 1- and 3-month assessments (spray 2).

Referral

At the 1- and 3-month follow-up assessments, the parents (guardians) were asked if their child had been referred to an ENT surgeon and whether or not surgery had been recommended (Appendices 7 and 8).

Adverse events

The parent (guardian) was asked at the 1- and 3-month assessments (Appendices 7 and 8) whether or not any of the following side effects/adverse events had occurred while his or her child was taking the spray: stinging in the nose, nosebleed, dryness and irritation at back of the throat, diarrhoea or cough. The first three of these were also available in the diary each week, for the parent (guardian) to say how much of a problem they had been if present (Appendix 10).

TABLE 3 *How the nine OM8-30 domains were used to give the six scores for the analyses*

Scores	Sections from OM8-30
RESPiratory symptoms	Respiratory Symptoms (B)
DEVelopmental impact	Behaviour (E) + Speech and Language (F) + School Prospects (H) + Parent Quality of Life (I)
PHYSical health	Global Health (A) + Respiratory Symptoms (B) + Ear Problems (C)
RHD	Reported Hearing Difficulties (D)
ACET[a]	Tympanometry-based predicted hearing level
Total OM8-30 impact	PHYS + DEV

a Air conduction estimated from tympanometry – uses 0–10 scale of severity from tympanometry, from mildest to most severe: A/A, A/C1, C1/C1, A/C2, A/B, C1/C2, C1/B, C2/C2, C2/B, B/B.

Health-care resources and other economic data

The health-care costs of importance to the economic evaluation were the direct costs associated with usual primary/GP care, costs associated with the interventions and other NHS costs incurred over the 9-month follow-up period.

The use of health-care resources for ear-related problems only, in both primary (e.g. number of GP surgery consultations, number of health visitor consultations, medications prescribed and their dosage) and secondary care (e.g. number of referrals, where to and why) were recorded by the RNs using the children's general practice medical records and a purposely designed form (Health Economics Evaluation form). This was carried out at baseline retrospectively for 15 months to take into account 12 months prior to the 3-month period of AM (Appendix 6) and at the 9-month assessment for the previous 9 months (Appendix 9), thus giving 2 years of data.

Health-related quality of life

A disease-specific impact on child and family score was to be derived from the OM8-30 questionnaire and used in the health economic analysis. In addition to this disease-specific measure, two generic utility instruments were introduced partway through the trial in order to enable a cost–utility analysis (CUA) to be conducted. These measures were completed at baseline and at both 3 and 9 months. The first instrument comprised the health utilities index (HUI) Mark 2 and Mark 3, 15-item questionnaire for proxy-assessed/administered completion, which includes the questions required to calculate utilities for both the Mark 2 and Mark 3 versions of the HUI instrument.

The second instrument comprised a version of the EuroQoL 5-dimension (EQ-5D) questionnaire. As the health-related QoL experienced by patients with OME will generally be good, the standard EQ-5D questionnaire (which comprises five dimensions, each with three levels) may not be sufficiently sensitive to detect differences between the treatment groups. Subsequently, the trial used a modified version of the child-friendly[72] EQ-5D questionnaire (referred to as EQ-5D$_5$ within this report) that incorporates five levels within each dimension through the insertion of additional tick boxes between the three levels included within the standard EQ-5D questionnaire (Appendix 13). This modification of the questionnaire was proposed by one of the main groups responsible for developing the EQ-5D instrument, which also suggested a number of possible methods for establishing a valuation tariff for this questionnaire.[73] Subsequent research has shown that five-level EQ-5D questionnaires have been found to be more sensitive for mild conditions,[74,75] have less of a ceiling effect[76] and have higher discriminative ability[76] – in terms of sensitivity both to changes over time and to differences between patient groups.[77]

Note: The EQ-5D and HUI were not used from the beginning of the study but after a protocol modification (see Changes to the original protocol).

Exit interview

At the 9-month assessment, the RNs used an open question exit interview (Appendix 9) to collect the parents' (guardians') and children's comments about being part of a trial, to ask them what treatment preferences they had and what they will do about the condition now the study had finished. Parents (guardians) and children were able to answer freely and the RNs recorded their responses word for word. These data were therefore qualitative and were analysed accordingly.

Intervention

Children meeting entry criteria and giving full informed consent were randomised to receive placebo or topical intranasal steroids given once a day for 3 months. Mometasone furoate 50 µg in each nostril (total daily dose 100 µg) was used because of its low systemic absorption and specified safety profile.[66–68] The trial was organised as an adjunct or extra to usual treatment, i.e. standard management, of such children by the practice (see consent form, Appendix 3).

Children and parents (guardians) received their first 1-month allocated treatment at the baseline visit and, upon return to the practice at 1 month, received the same allocated treatment for a further 2-month period (irrespective of tympanometry findings).

The appropriate method of using the spray was demonstrated at the baseline visit by the trained RN to parents (guardians) and children. The parent's (guardian's) or child's use of the spray was observed and assessed by the RN so that the maximal dose to the posterior nasal space was achieved. This was intended to produce maximal local decongestant/anti-inflammatory effects on the posterior nasal airway (the size of which is a

known risk factor for persistence) and on adenoidal tissue. This was supplemented with a succinct illustrated patient information sheet on aims, use, safety and side effects. Opportunity was given for questions/problems to be dealt with firsthand by the RNs and thus improve overall compliance. A once-daily dosing schedule was used to encourage compliance. There was no pre-specified time of day for the dosing but rather child co-operation and established routines for taking the spray were encouraged.

As mentioned, compliance was evaluated by measuring before and after individual bottle weights at 1 and 3 months. Non-directive questioning was used at telephone follow-up after several days, e.g. 'Have you any concerns or experienced any problems with this medication?', and based on a modified brief adherence questionnaire[73] (Appendices 6 and 7). Two secondary care trials have achieved effective compliance for 3 months and 2 years respectively, using topical steroids in children.[60,61] Good communication and education at baseline and 1 month ensured adherence. Any treatment schedule longer than 3 months would introduce greater complexities in relation to administration, would increase side effects, might delay important management decisions after an accepted period of AM, and does not make use of the natural resolution effects at 3 months.[16,19]

Sample size

The original protocol power calculation specified that for a standard two-sided alpha of 0.05 and a beta of 0.2 assuming (1) 21% resolution of effusions in the intranasal steroid group, (2) 10% resolution in the placebo group, and (3) a 15% dropout rate and 3% non-interpretable tympanograms, 388 children were required.[60,79] It was proposed that this sample would allow detection of modest (~15%) differences in actual surgery rates in referral-based models. Assuming only ~40% of an enrolled sample are randomised due to natural resolution effects, refusals and immediate referrals, then just over 1000 children needed to be identified in practices with bilateral OME confirmed. No study data were available from primary care samples so it was not possible to more accurately predict effect sizes for resolution in the treated group than for placebo in this setting. Because resolution is likely to be significantly higher in primary care (spectrum bias) this sample size estimate was conservative. The tympanometric criteria used for the above power calculation[60] were also more conservative than are usually used to define cure.[79] The HTA therefore agreed to also allow for type C1 as cured,[69,70,79] so the original power calculation was subsequently revised using community prevalence data on A and C1 types.[19] Two hundred and forty children were required, assuming a 15% dropout rate and 3% non-interpretable rate for an alpha of 0.05 and a beta of 0.2 assuming 28% tympanometric resolution in the topical steroid group and 12% in the placebo group.[19] Differences of 15% or less for tympanometric outcomes are not likely to be clinically significant as tympanometry is a disease measure with only a moderate PPV of 0.49[80,81] for a relevant clinical outcome, the pure tone hearing level, and is thought by specialists to be over-sensitive to clinical intervention. The very high prevalence of OME (over 80%) and high relapse rate (24% from this study) thus require moderate tympanometric effects, at least in the 15% range, for a community treatment to be deemed clinically beneficial. Tympanometry is justified because it is probably the best objective measure to detect any treatment effect; even subclinical effects and audiometry is unreliable in a primary care setting.

Data entry

Data were sent by the RNs to the co-ordinating centre (University of Southampton) and entered into a specifically designed Microsoft ACCESS database. Data were entered continuously throughout the study period. Data entry was checked regularly and data were rechecked during the cleaning process. Missing data were, where possible, retrieved from the RNs.

Analysis

Primary outcome

The primary analysis was carried out on an intention to treat (ITT) basis with children as the unit of analysis rather than ears. The proportion of children cleared of bilateral effusions at 1 month in the two groups was compared using a logistic regression model with adjustment for four covariates:

1. season (January/February/March versus the rest of the year)
2. age at randomisation (continuous in months)
3. atopy (defined as the combination of asthma/eczema/hay fever that best predicts outcome

in a blind analysis of children ignoring randomisation)
4. clinical severity {defined as the first principal component of the baseline variables: frequency of surgery attendance in last 12 months for ear problems; tympanogram readings; age at first episode of hearing infection/problem; total reported episodes of ear problems over the last 12 months; adenoidal symptom score [respiratory symptoms (RESP) score from the OM8-30] – identified in an analysis of these variables ignoring randomisation group}.

Effect modification

Interaction tests were carried out between randomisation group and each of (a) age, (b) atopy and (c) clinical severity score – defined as above. Interaction tests were carried out using the Likelihood Ratio Test on logistic regression models with and without each interaction (a–c, defined above). In the event that these were statistically significant ($p < 0.05$), separate results would be presented in subgroups.

Secondary outcomes

The proportion of children cleared of bilateral effusions at 3 and 9 months in the two groups was compared using a logistic regression model with adjustment for four covariates as for the primary outcome.

Results were expressed as ORs with 95% CIs. Subgroup results were not undertaken, as the interaction tests in (b) above were not statistically significant. Differences between active and placebo groups in reported hearing difficulties (RHD), respiratory symptoms (RESP), hearing loss (ACET), physical health and sleep score (PHYS), developmental (DEV) and total OM8-30 scores were investigated using non-parametric tests.

For the main analyses, missing data were assumed to be missing at random and therefore subjects with missing data were not included in analysis. The effect of AM or not was investigated using chi-squared tests for the main tympanometric outcomes at all the time points.

SPSS versions 12.0 and 16.0 were used for the statistical analyses of all clinical outcome measures.

All statistical analyses on cost and resource use (Chapter 5, Analysis of resource use and costs) were performed using Microsoft EXCEL 2003, and the difference in cost and resource use between the study arms was tested using independent-sample *t*-tests, assuming unequal variances. All tests were two-tailed and an alpha value of 0.05 was used. Mean total health-care costs, including values imputed using multiple imputation, were calculated using the same methods for utilities imputed using multiple imputation (see point 2 below).

Statistical tests on health utilities (Chapter 5, Analysis of utility measures) were conducted using three different methods:

1. *Analysis of utilities of quality-adjusted life-years (QALYs) based on a complete case analysis or using mapped utilities* Treatment groups were compared with respect to health utilities using independent-sample *t*-tests assuming equal variance, which were conducted in STATA Version 10.0. Comparison of the treatment groups with respect to categorical end points (e.g. the proportion of patients with no problems on any given scale) was tested using chi-squared tests, including Yates' correction in cases of 1 degree of freedom (df), which were conducted in Microsoft EXCEL 2003.
2. *Analysis of utilities, QALYs or total health-care costs using data sets in which missing data were estimated using multiple imputation* Standard errors (SEs) around the means for each treatment group were calculated using Equation (1), later in this chapter. The SEs around the mean difference between the two study arms were calculated for each imputed dataset based on $SE^2_{difference} = SE^2_{treatment} + SE^2_{placebo}$; these SEs for the five imputed data sets were used to calculate the overall SE around the difference in means using Equation (1). In both cases, *p*-values were based on *t*-tests, whereby *t* equalled mean divided by SE and *p* was calculated based on the *t*-distribution in Microsoft EXCEL 2003.
3. *Analysis of utilities using a regression-based adjustment for utilities* Linear regression analyses to adjust for baseline utilities were conducted using the 'regress' command in STATA Version 10.0, which conducts ordinary least squares (OLS) regression. In cases in which data imputed using multiple imputation were analysed in this way, the 'micombine' option in STATA was used to generate estimates of coefficients and *p*-values that combined all five datasets and allowed for the uncertainty around imputed values.

All tests were two-tailed and used an alpha value of 0.05. The statistical methods used in the analysis of cost-effectiveness are described below.

Primary objective of economic research

The economic evaluation aimed to assess the cost-effectiveness of topical intranasal steroids in the management of OME compared with standard care (without use of steroids) based on the data collected within the trial.

Steroid treatment itself is likely to have at least two economic research aspects, which both relate to clinical effectiveness. The first is the short-term side effects and relief from primary symptoms and direct consequences of the condition on costs and health-related QoL. The second is the long-term effects in terms of reduced disability and any long-term adverse reactions from treatment. This study assessed only short- to medium-term outcomes, although the protocol allowed for extrapolation of the short-term effects and costs over a longer time horizon if the results had demonstrated a difference in short-term outcomes. This longer term modelling would have been based on the natural history of the disease and additional evidence from the literature in the event that the trial revealed significant benefits for intranasal steroids.

The analysis took the perspective of the NHS. Costs incurred by children's families or education services were excluded from the analysis. Data on the quantity and cost of resources for personal and social services use were not collected due to the practical difficulties of such an analysis.

Two main analyses of incremental cost-effectiveness were conducted. The first analysis comprised a cost-effectiveness analysis (CEA) calculating the incremental cost per additional child with resolution of OME at either 1 or 3 months, while the second comprised a CUA calculating the incremental cost per QALY gained through treatment.

Note A protocol modification was made that involved changes to the collection of the health economic data. The data collection, calculation and analyses are described in Health economic evaluation – data collection, calculation and analysis.

Interim analyses

The Data Monitoring and Ethics Committee (DMEC) performed an interim analysis in April 2006. The committee agreed that the study should continue but requested another interim analysis the following year. In April 2007 a second interim analysis was performed by the DMEC. At this time 217 children had been randomised and the protocol stated that recruitment would finish by April 2007. The outcome of this second interim analysis would determine whether or not a protocol change was required to extend the period of recruitment. The analysis showed a significant negative result that, according to the DMEC, would be very unlikely to be changed by recruiting more children on to the study; therefore, after discussion with the Trial Steering Committee (TSC), the study closed to recruiting as of April 2007. As this was the date stated in the protocol, the study did not therefore end prematurely, although it failed to reach the 240 sample size specified.

Changes to the original protocol

In response to the rate of recruitment, parent (guardian) feedback, loss of the health economist and decisions by the TSC, the original protocol was revised on two occasions (see Appendix 11 for earlier versions of the protocol).

Analysis plan (version 2, dated 16 June 2004)

Following discussion at a TSC meeting in February 2004, a revised analysis plan was written into the protocol – the previous multiple subgroup analyses were removed to reduce chances of false positive findings and need for Bonferroni corrections. The primary and secondary outcome analyses were clearly restated together with potential effect modifications (interactions with age, gender, atopy and clinical severity only). Clinical severity as a first principal component could be clinically useful and was retained in the plan.

Removal of active monitoring (version 3, dated 5 May 2005)

By 18 months into the study it was evident that the rate of recruitment had been slower than expected. This was largely due to an initial 3-month delay (June–August 2003) pending a successful appeal

against an initial rejection decision by COREC [Central Office for Research Ethics Committees; now NRES (National Research Ethics Service)], resulting in a 3-month delay in recruiting general practices and RNs (RNs did not start inviting children until January 2004). At the end of 2004 there was a further 3-month delay as a result of the MRC financial restructuring of payments to practices.

The decision was made to relax the rigorous entry criteria and, in line with parent (guardian) and child feedback, GP treatment behaviour and TSC support, the 3-month period of AM was removed from the study design. Thus the inclusion criteria changed:

- Children aged 4–11 years.
- Attendance at the GP surgery with at least one episode of a related ear problem in the previous 12 months.
- Failing tympanometry, i.e. confirmed bilateral OME (B/B or B/C2) tympanograms.

The removal of AM impacted on the case report forms. The Beginning of watchful waiting (AM) form (Appendix 4) was no longer required and the End of watchful waiting (AM) form (Appendix 5) was changed to the First Screening form (Appendix 12).

Collection of more detailed health economic related data (version 3, dated 5 May 2005)

The removal of AM coincided with the departure of the study's original health economist. Dr Stavros Petrou from the University of Oxford was employed as the replacement and, on his suggestion, changes were made to the health economic capture forms.

The Costs to Parents form was changed to collect data on health-care use as reported by the parent (guardian). This revised form was used at baseline (Appendix 13) and the 9-month assessment (as previously, but it was also included at the 3-month assessment (Appendix 13). At baseline this form covered the previous 12 months, at the 3-month assessment it covered the previous 3 months and at the 9-month assessment it covered the previous 6 months, therefore it provided data over 21 months. The baseline Costs to Parents form also included sociodemographic questions; parents' (guardians') educational attainment, their marital status, their child's ethnicity, whether English is their first language and their gross family income. These forms at baseline, 3-month and 9-month assessments no longer directly considered the impact of OME on the children's lives, this was now solely obtained through the diaries.

The Health Economics Evaluation form at baseline and the 9-month assessment was also changed. It was disaggregated to cover health-care resource usage for non-ear-related problems as well as ear-related ones. The baseline form looked back over the 12 months before randomisation (Appendix 13), and the 9-month assessment form covered the 9 months the child had been in the study (Appendix 13).

Two new measures were incorporated into the study from this point, the EQ-5D instrument (Appendix 13) and the HUI (Appendix 13). Cost evidence was synthesised with utility data from these two multi-attribute utility measures, in order to estimate the incremental cost per QALY gained attributable to topical intranasal steroids.

The EQ-5D and HUI were completed by the parent (guardian) at baseline, 3-month and 9-month assessments, when possible, with their child's help.

Table 4 summarises the initial and revised schedules of assessments carried out at each time point. When AM was removed and the revised assessment forms brought in, some children had already been randomised, therefore when they came to their 3- and 9-month assessments the RN used the revised forms. This meant that for some randomised children who had been in the 'with AM' part of the study there were some data that were not collected on the other randomised children who had been in AM. These data, where possible, were used for the health economic analyses.

Health economic evaluation – data collection, calculation and analyses

Collection of resource use data

Data were collected about all significant health service resource inputs over the 9-month time horizon of the study. The study data forms provided a record of all appointments with community health-care providers; medications prescribed for the treatment of OME; medication prescribed for other reasons; investigative tests carried out; and hospital inpatient and outpatient service use, which included length of stay, reasons

TABLE 4 *Summary of research assessments*

	With AM				Without AM			
	Baseline	**1 month**	**3 months**	**9 months**	**Baseline**	**1 month**	**3 months**	**9 months**
Assessment measures	+	+	+	+	+	+	+	+
Ear problem checklist	+				+			
Costs to parents form	+		■	+	◇		+	◇
OM8-30 questionnaire	+		+	+	+		+	+
Health economics evaluation form	+			+	◇			◇
Adherence form	+	+			+	+		
Diary	+	+			+	+		
EQ-5D				■	+		+	+
HUI				■	+		+	+
Exit interview				+				+

+, present; ◇, present in study with and without AM, but forms are different in the two parts of the study; ■, some data collected (see description of table above).

for admission or appointment and any operations carried out, as well as the name of the hospital provider, its location, the duration of contact, and the ward or clinic attended. These data were obtained through two principal means. First, the RN in the GP practice of each child retrospectively completed forms relating to the child's attendances and prescription of medicine, as well as referrals to hospitals and other community health service providers over the 9-month follow-up period (Appendices 6, 9 and 12). Second, forms were completed by parents of each child relating to their child's use of medications and hospital and community health services (Appendices 6, 9 and 12). These parent-completed data were used to validate the information collected directly by the RNs, as previous research had indicated that parents are relatively accurately in their recollection of their children's use of health services.[82] When the parental reports of hospital and community services were compared directly with the data collected by the RNs from the GP practice data collection systems, parental reports tended to underestimate the numbers of admissions, referrals and contacts. It was therefore decided to use the resource use data collected by the RNs in the base-case analyses.

Unit costs

Unit cost for resources used by children who participated in the study were obtained from a variety of primary and secondary sources, with the majority obtained from secondary sources (Appendix 14). All unit costs employed followed recent guidelines on costing health and social care services as part of economic evaluation.[83] Secondary information was obtained from ad hoc studies reported in the literature.

Unit costs of community health and hospital costs were largely derived from national sources[84] and took account of the cost of the health professionals' qualifications. Some costs were valued using the NHS reference costs, a catalogue of costs compiled by the Department of Health in England.[85] Drug costs were obtained from the *British National Formulary* (BNF).[86] Costs for individual preparations were used as well as costs for chemical entities, i.e. drugs were grouped by chemical entity and unit costs for these chemical entities were calculated. All of the costs are expressed in pound sterling and valued at 2006–7 prices. Unit costs were combined with resource volumes to obtain a net cost per child covering all categories of hospital and community health service costs.

Calculation of utilities and quality-adjusted life-years

The responses to the utility measures collected during the trial (HUI2/3 and EQ-5D$_5$) were converted into utilities using standard tariffs/weightings. The standard multiplicative multi-attribute utility functions were used for HUI2 and HUI3.[87,88]

As described in Health-related quality of life, the study used a five-level child-friendly version of the EQ-5D (the EQ-$5D_5$) in order to reduce the ceiling effect commonly to be observed when the three-level questionnaire is used in mild conditions. Although there is currently no formal 'tariff' for the EQ-$5D_5$ questionnaire used in the trial, Kind and Macran[73] have suggested a number of different possible methods for calculating utilities for this questionnaire: (1) assuming that the coefficients for the intermediate levels lie half-way between those for the three levels for which data exist; (2) rounding responses up or down to the nearest of the main three levels; and (3) using a new set of coefficients generated from a data set for which both measures were used based on the assumption that all levels are equally spaced. The first method (applying the standard N3 tariff,[89] while assuming that intermediate levels have coefficients mid-way between those of the standard three levels) was used for the analysis of EQ-$5D_5$ in order to make use of the potential increase in sensitivity that is conferred by the five-level questionnaire, while minimising the number of assumptions required.

For the base-case analysis, utilities were based on the HUI3 as this instrument has been widely used and validated in children,[90–92] and is likely to have greater sensitivity and a less pronounced ceiling effect than the EQ-$5D_5$. Sensitivity analyses were conducted using utilities based on the HUI2 and EQ-$5D_5$ questionnaires.

No utility data were collected prior to the protocol changes that removed the AM period and enabled the collection of further health economic data. Furthermore, utility data were also missing for a large number of children recruited after the protocol changes, such that overall around 45% of all potential utility measurements were missing. Subsequently, analyses were conducted to 'map' or 'cross-walk' responses on the OM8-30 generic measure onto the utility measures used in the trial. These analyses are described in more detail in Appendix 15. Briefly, a range of regression models were investigated to identify the model that best predicted children's utility based on their responses/scores in the OM8-30 questionnaire and key demographic characteristics. The choice of model was based predominantly on the mean absolute error (MAE) between predicted and observed values, but was also informed by the proportion of predictions that were more than 25% from the actual values, statistics on goodness of fit [R^2, root mean squared error (MSE) and information criteria statistics] and the degree of consistency and logical plausibility of coefficients. The best model was a linear regression with suppressed constant that predicted children's disutility based on their scores for the nine OM8-30 facets, plus predicted hearing level based on tympanometry [ACET (air conduction estimated from tympanometry) from OM8-30]. However, an OLS model with suppressed constant that predicted children's disutility based on their scores for the DEV and PHYS domains of the OM8-30, RHD, age, sex and predicted hearing level also fitted the data well and was used in a sensitivity analysis. The model was fitted to a randomly selected subset comprising 75% of the observations for which data from both OM8-30 and utility measures were available; the remaining 25% of observations were used to test the model generated. The primary analysis was conducted using the HUI3 as the dependent variable, although analyses were repeated for the HUI2 and EQ-$5D_5$.

The utilities predicted from the OM8-30 mapping algorithm were used as additional predictors in the multiple imputation (see below). Mapped values were also used directly in sensitivity analyses that used mapped values in place of data directly collected from completion of utility measures in cases in which no utility data were available.

The number of QALYs accrued over the 9-month follow-up period was calculated using linear interpolation (*Figure 2*). In sensitivity analyses in which multiple imputation was not conducted, missing data at 3 months were overcome by assuming that children's utility changed in a linear fashion between baseline and 9 months, while missing data at 9 months were overcome by assuming that the child's utility at 9 months was the same as that at 3 months. Children lacking utility data at baseline and those lacking both 3- and 9-month utilities were excluded from such analyses.

Preliminary statistical analyses highlighted an imbalance in baseline utility values between the two treatment groups. It was therefore necessary to adjust utility values to allow for this imbalance in order to generate an unbiased estimate of treatment effect. For the purposes of the CUA, this adjustment was conducted by simply subtracting each child's baseline utility value from their on-treatment utilities before calculating QALYs as described above.[93] This method effectively indexes the utilities relative to baseline and calculates the QALY gain or loss that each child has experienced

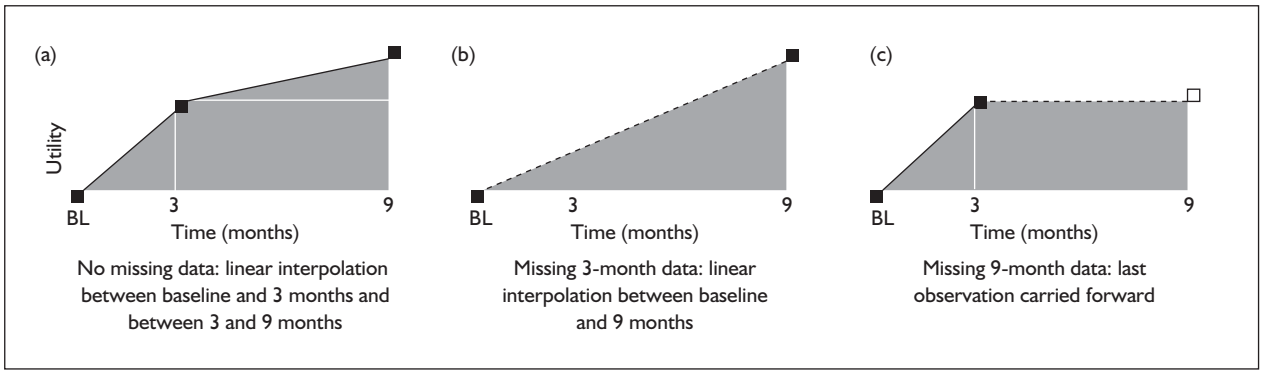

FIGURE 2 *Methods used to calculate QALYs: the area shaded grey represents the QALYs accrued after adjustment for baseline utility. The methods shown in panel (a) were used to calculate QALYs for all children in analyses using data derived from multiple imputation and for those children who had utility data at all three time points in analyses that did not use multiple imputation.*

during the study period compared with the QALYs that would have been accrued if the child had remained at their baseline level for the entire study period. For example, if a patient had a baseline utility of 0.7, which increased to 0.8 at 3 months and 0.9 at 3 months, their baseline-adjusted QALYs would be 0.0875: $\{[(0 + 0.1)/2] \times 0.25$ years$\}$ + $\{[(0.1 + 0.2)/2] \times 0.5$ years$\}$ relative to baseline, compared with 0.6125 unadjusted QALYs: $\{[(0.7 + 0.8)/2] \times 0.25$ years$\}$ + $\{[(0.8 + 0.9)/2] \times 0.5$ years$\}$. This method of adjusting for baseline utilities was used in the base-case economic evaluation in order to facilitate use of bootstrapping within the CUA.

In order to more accurately assess the statistical significance of any differences in the QALYs accrued between the two groups, while avoiding the problems of regression to the mean, an alternative method of baseline-adjustment of utilities was used alongside the simple subtraction method within the QALY analysis. The regression/ANOVA (analysis of variance) approach was conducted by running a simple linear regression to assess the impact of treatment and baseline utility on the total (unadjusted) QALYs accrued by each child.[93] The coefficient around the treatment dummy variable was used as an estimate of the incremental QALY gain from treatment. However, this approach was not used within the CUA.

Methods for dealing with missing data

Multiple imputation was used in the base-case analysis in order to overcome any biases associated with missing data and fill in all gaps within the data on costs, clinical end points and utilities. Multiple imputation was conducted using the 'ice' command within STATA 10.0, which employs widely used statistical techniques which have been described in previous work.[94,95] In order to allow for the highly skewed distribution of utilities and (to a lesser extent) costs, disutilities and costs were transformed onto a log scale using the transformation $A_{Trans} = [\ln(A + 0.00001)]$, in which A is the untransformed value and ln is the natural logarithm. The constant 0.00001 is used to enable values that are equal to 0 to be transformed onto a logarithmic scale.

In order to make use of the fact that OM8-30 scores correlate with utility (Appendix 15), an algorithm was developed to estimate utilities based on responses to the OM8-30 (Appendix 15). The predicted disutility that the child would be expected to have at each time point based on his or her OM8-30 facet scores was included in the imputation analysis in addition to demographic characteristics, costs and utilities. This predicted disutility was included in the analysis in preference to the OM8-30 facet scores, as it was anticipated that including 30 additional variables (HL and the nine OM8-30 facet scores that were observed at each of the three time points) would prevent estimation of any reliable imputation model. No transformation was applied to the predicted disutilities, as the predictions followed a symmetrical and approximately normal distribution; furthermore, predicted negative disutilities were left as negative values in order to preserve the distribution and reflect the OM8-30 responses more accurately.

The following variables were included in the imputation analysis:

- age: no missing data
- sex: no missing data
- study protocol (dummy for whether the child was recruited before or after the protocol change that removed the AM period): no missing data
- treatment allocation (dummy for whether the child received active treatment or placebo): no missing data
- total cost based on retrospective review of children's medical records (transformed on a log scale; match option used)
- total cost based on parents' costing questionnaire (transformed on a log scale; match option used)
- HUI3 utility at baseline (transformed on a log scale; match option used)
- HUI3 utility at 3 months (transformed on a log scale; match option used)
- HUI3 utility at 9 months (transformed on a log scale; match option used)
- HUI2 utility at baseline (transformed on a log scale; match option used)
- HUI2 utility at 3 months (transformed on a log scale; match option used)
- HUI2 utility at 9 months (transformed on a log scale; match option used)
- EQ-5D utility at baseline (transformed on a log scale; match option used)
- EQ-5D utility at 3 months (transformed on a log scale; match option used)
- EQ-5D utility at 9 months (transformed on a log scale; match option used)
- predicted HUI3 disutility at baseline that was calculated using the HUI3 facet model described in Appendix 15 (match option used). A mapping model was used to predict HUI3 utility based on patients' facet scores on the OM8-30 questionnaire, based on a randomly selected subset of 75% of patients in the GNOME study who completed the HUI3 and OM8-30 questionnaire fully
- predicted HUI3 disutility at 3 months that was calculated using the HUI3 facet model described in (match option used)
- predicted HUI3 disutility at 9 months that was calculated using the HUI3 facet model described in (match option used)
- composite clinical outcome (dummy variable indicating whether the child had been cured at 1 or 3 months).

The match option was used for multiple imputation, as even the log-transformed utility and cost variables had significant skew and differed significantly from a normal distribution. The match option works by generating predicted values for each child for each variable (including those children with complete data) based on linear or logistic regression functions; the predicted value for each observation with missing data is then compared with that for children who have a value recorded for the variable in question, and assumes that the value in question is equal to the closest match. This constrains the imputed values to be within the range of values that were observed and is less dependent on assumptions of normality. Standard imputation (without using the match option) produced implausible values for costs and utilities, even after log transformation of the data; in particular, utility values well below zero were imputed for many children, despite the fact that no children in the sample had HUI3 utilities below zero. By contrast, when the match function was used, all values generated were plausible, and the distributions, means and standard deviations (SDs) of the imputed data were similar to the observed values.

Other than use of the match option, the default assumptions for the 'ice' command were used for the imputation analysis; this involved use of logistic regression for the composite clinical end point, and linear regression for all other variables. Five imputed data sets were generated. The values generated within each imputation were transformed back to a natural scale where necessary using the reverse of the transformation formula shown above. Children's utility was assumed to be one if a value of one was imputed for the perfect health variable and was otherwise based on the value imputed for the HUI3 utility. Bootstrapping was conducted on all five data sets generated in the multiple imputation in order to allow for uncertainty between imputed datasets when calculating 95% CI and the probability that treatment is cost-effective[94] as described in Calculation of cost-effectiveness ratios.

However, several different approaches to dealing with missing data were investigated within sensitivity analyses. Firstly, a complete case analysis was conducted, whereby the results of multiple imputation were not used and only children with complete data on costs and outcomes were included in the analysis. In the CUA, the complete case analysis included only patients with complete

cost data who completed the HUI3 questionnaire at baseline and both 3 and 9 months after start of treatment; the CEA complete case analysis included only patients with clinical outcome data at either 1 or 3 months who also had complete cost data. Secondly, two analyses were conducted in which mapped estimates for HUI3 utility were included alongside observed utility values; these analyses included only those children with complete resource use data and utility data at baseline and at either 3 or 9 months from HUI3 or the OM8-30 mapping exercise. Thirdly, the impact of alternative imputation methods was investigated for the CEA in the form of a mean imputation analysis (whereby all missing data on costs or clinical outcomes were assumed to equal the mean value for the relevant treatment group); a best case analysis (whereby all children missing clinical outcome data were assumed to have been cured); and a worst case (or ITT) analysis (whereby all children with missing clinical outcome data were assumed to not have been cured).

Calculation of cost-effectiveness ratios

As described above, the primary clinical outcome measure for the study was the presence or absence of OME (i.e. cured or not cured) 1 month after starting the course of intranasal steroids, with adjustment for covariates. Clinical outcome data for the study were collected at 1, 3 and 9 months. However, the 9-month outcome data were not used for the CEA. The rationale for this came from previous research,[96] which has shown that children who are susceptible to OME tend to have more separate episodes of effusion rather than an increased overall duration of episodes. Such children are primarily distinguished by the likelihood with which they acquire the disease than by their ability to recover from it. Thus, any outcomes observed beyond 3 months might not be due to the active treatment, but could be attributed to the fluctuating nature of the condition. Hence, the 9-month data were not used because of this highly recurrent nature of OME.

Instead of using 9-month data, the base-case CEA used a composite outcome measure that was created using the 1- and 3-month data. This composite measure was created by assuming that if a child was cured of OME at either 1 or 3 months, they were considered cured and if a child still had OME at both time points, they were considered not cured. For children missing data at one of these time points, outcomes were based on outcomes at the time point at which data were available.

This end point was chosen in preference to the primary clinical end point (cure at 1 month adjusted for covariates) as it has a number of advantages. Firstly, the composite end point combines two different trial end points by allowing for children who are cured by the end of treatment as well as cures occurring by 1 month. Furthermore, this end point requires less imputation of data than cures by a single time point. It is common for trial-based economic evaluations to use a different (generally longer) time horizon than clinical end points and in this case, it would not be practical to use exactly the same primary end point as that used in the clinical analysis (the proportion of children cured by 1 month, after adjustment for covariates) without adopting a net benefit framework and greatly complicating the analysis. However, the choice of clinical outcome used in the CEA was varied in sensitivity analyses, which calculated cost-effectiveness based on outcomes at 1, 3 or 9 months.

For both the CEA and the CUA, differences in mean costs and effects between the groups were calculated. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in costs (ΔC) divided by the difference in effects (ΔE). For the CEA, cost-effectiveness was expressed as the incremental cost per case of OME cured. The CUA calculated the cost per QALY gained, with QALYs being calculated based on the methodology described above.

Both the CEA and the CUA took a 9-month time horizon for costs within the base-case analysis, as this comprised the maximum duration of the trial and ensures that any difference in costs or health-care resource use that results from the intervention was captured. No discounting of future costs or benefits was applied as the time horizon was less than 12 months.

To account for the skewed nature of the cost and utility data, non-parametric bootstrap estimation was used to calculate the probability that treatment is cost-effective and derive the 95% CIs for mean incremental costs and benefits between the placebo and treatment groups.

For the base-case analysis and all subgroup or sensitivity analyses that included data that were imputed using multiple imputation, the five

imputed data sets generated using multiple imputation were bootstrapped separately in order to allow for the uncertainty between (as well as within) imputed datasets.[94] For the base-case analyses of both the CUA and the CEA, 5000 bootstrap replicates were conducted for each of the five imputed data sets; 1000 bootstrap replicates were conducted for each data set within all sensitivity and subgroup analyses except for those that involved a complete case analysis or imputation techniques other than multiple imputation (which used 1000 bootstrap replicates for the single data set used in those analyses).

The mean costs and mean benefits (the mean number of QALYs or mean number of children cured) were based on the average of the raw data for all imputed datasets, which was equal to the mean of the means from each of the five imputed data sets. In order to allow for both sampling uncertainty and uncertainty around imputed values, the SEs around the mean costs, mean benefits and the mean difference in costs/benefits were calculated using the equation described by Briggs *et al*.[94]

$$\hat{\text{var}}(\hat{\theta}) = \frac{1}{M}\sum_{i=1}^{M}\hat{\text{var}}(\hat{\theta}_i) + \left(1+\frac{1}{M}\right)\left(\frac{1}{M-1}\right)\sum_{i=1}^{M}(\hat{\theta}_i - \hat{\theta})^2 \qquad (1)$$

where M represents the number of imputed data sets generated (in this case five), $\hat{\theta}_i$ represents the parameter of interest for data set i, $\hat{\text{var}}(\hat{\theta})$ represents the variance (SE^2) around the parameter of interest across all data sets (including both variability within and variability between data sets) and $\hat{\text{var}}(\hat{\theta}_i)$ represents the within-data set variability for data set i.

The SEs calculated using this equation were used to calculate 95% CI based on a t-distribution with df equal to $(M-1)(1+r^{1-})^2$.[94]

The proportion of variability that was due to uncertainty around imputed values was calculated by dividing the term

$$\left(1+\frac{1}{M}\right)\left(\frac{1}{M-1}\right)\sum_{i=1}^{M}(\hat{\theta}_i - \hat{\theta})^2 \qquad (2)$$

by the total variance $\hat{\text{var}}(\hat{\theta})$.

Estimates of the probability of treatment being less costly, more effective, dominant or dominated relative to placebo at different ceiling ratios were calculated across all bootstrap replicates for all five imputed datasets.

Uncertainty around the conclusions about whether or not treatment was cost-effective was represented in the form of a cost-effectiveness acceptability curve (CEAC).[97] This shows the probability of intranasal steroids being cost-effective at a range of maximum values (termed ceiling ratios, R_c) that decision-makers may be willing to pay for an additional case of OME cured or an additional QALY. The CEACs and the probability of treatment being cost-effective were calculated based on the proportion of simulations (across all five imputed data sets) with positive net benefit at a range of ceiling ratios. CIs and SEs around the mean costs and benefits were calculated by assuming normality. The bootstrap simulations of the ICER were plotted on the cost-effectiveness plane to give a non-parametric illustration of the joint density of costs and effect differences.

In cases in which the results of multiple imputation were not used (e.g. for the complete case analyses and analyses using mapped utilities), bootstrapping was conducted on a single data set, using 1000 bootstrap replicates. In these analyses, SEs and CIs were calculated using a standard parametric approach and CEACs and the probability of treatment being cost-effective was calculated across all bootstrap replicates run.

Extrapolation and additional analyses

The trial protocol allowed for the option of constructing decision-analytical models to extrapolate the results of the trial beyond the 9-month time horizon using additional data taken from the literature to calculate the long-term impact of treatment on costs and benefits, including allowing for the incidence of disability and surgery. However, given that the analysis found no evidence that treatment conferred significant clinical benefits, the trial results were not extrapolated beyond the end of the trial.

Sensitivity and subgroup analyses

In addition to the base-case analysis, a number of sensitivity and subgroup analyses were conducted for both the CEA and the CUA.

Two sensitivity analyses were common to both CEA and CUA:

1. basing costs on parents' (or guardians') responses to resource use questionnaires completed at 3 and 9 months
2. adding in the cost of tympanometry at baseline for all children.

Seven sensitivity analyses specific to the CEA included:

1. mean imputation of costs and clinical outcomes for children for whom data were missing
2. estimating cost-effectiveness in terms of incremental cost per case of OME cured at 1 month
3. estimating cost-effectiveness in terms of incremental cost per case of OME cured at 3 months
4. estimating cost-effectiveness in terms of incremental cost per case of OME cured at 9 months
5. worst case/ITT analysis: assuming all children with missing outcome data were not cured at either 1 or 3 months
6. best case analysis: assuming all children with missing outcome data were cured at either 1 or 3 months
7. complete case analysis: including only those patients with no missing data on the composite end point or on costs.

Sensitivity analyses 1 and 5–7 did not use the results of multiple imputation and were therefore based on 1000 bootstrap replicates of a single data set. Analyses 2–4 used a different run of multiple imputation in which the composite end point was not imputed, but the clinical outcomes at 1, 3 and 9 months were included as three separate variables. This was conducted to minimise the number of variables used in the imputation run used for the base-case analysis (which was necessary to ensure that stable and realistic estimates of missing data on utilities, costs and composite clinical outcomes were generated. Other than this change to the clinical outcome data, this run of multiple imputation was conducted using the same methods as the base-case imputation analysis, although outcomes differ slightly due to the change in the variables used.

A further six sensitivity analyses relating to the calculation of QALYs were conducted for the CUA:

1. use of utilities based on responses to the $EQ\text{-}5D_5$ questionnaire
2. use of utilities based on responses to the HUI2 questionnaire
3. making no adjustment for baseline utilities
4. complete case analysis: including only those patients for whom the HUI3 questionnaire was fully completed at all three time points and who had complete cost data
5. using HUI3 utilities predicted using the mapping model of OM8-30 facet scores that is described in Appendix 15 instead of values estimated using multiple imputation
6. using HUI3 utilities predicted using the mapping model of OM8-30 domain scores (plus age and sex) that is described in Appendix 15 instead of values estimated using multiple imputation.

The following six sets of subgroup analyses were conducted for both the CEA and the CUA, in which the incremental costs per additional unit of health outcome were calculated for the following subgroups of children:

1. children younger/older than 6.5 years at baseline
2. boys/girls
3. children with/without atopy symptoms at baseline
4. children with severe/non-severe disease at baseline, defined by whether the child's clinical severity score was in the worst 25% of the cohort; this equated to cases with clinical severity scores of 0.62 or higher being classed as severe
5. children recruited to the trial in January, February or March, compared with those recruited between April and December
6. with/without AM (i.e. before/after the protocol changes described in Changes to the original protocol).

All of the subgroup analyses should be considered post hoc as they were not pre-specified. However, this list comprises an exhaustive list of the subgroups investigated and no subgroup analyses that were conducted are omitted from this report.

Chapter 3

Recruitment rates, data collection and follow-up rates

Recruitment of practices

GP practices were recruited in four rounds (2003–6). *Table 5* shows the numbers recruited and lost each year. Ninety-nine practices were recruited in total with no more than 64 being active at any one time, the annual mean number active over the study was 51 practices. Six practices had two RNs and two RNs covered two practices each. RNs/practices left the study for a variety of reasons: retired (2), new job (4), practice withdrew, e.g. could not give RN time to do the study (3), exhausted the population of children in their catchment area to make it cost-effective to remain in study (5) and personal reasons, e.g. maternity leave, close family death/illness, time constraints (30). There were 65 tympanometers available to the study and each practice needed one, therefore this was the limiting factor in the number of practices that could be active at any one time.

Following recruitment, new RNs were trained as mentioned in Chapter 2. In 2003, two training days took place in September and October; in 2004 there were four training days in September, October, November and December; in 2005 there were three training days all in September; and in 2006, three training days took place, one in August and two in September (one of which was held in Southampton as there were several practices recruited from the surrounding area and so it was more cost-effective). A training update for the 2003–5 recruited RNs was offered on two days in January 2006, the take-up was 43% (27/63). The lead GP in each practice was the principal investigator, but the GP input into the study was fairly minimal, simply checking a list of children generated by the RN to determine whether or not they could or should be approached.

Many of the RNs were also participating in other MRC General Practice Research Framework (GPRF) studies. Twenty-three per cent of practices did not invite any children to be screened; of the 76 practices that did screen children, 36% stated that they found no children that were eligible for randomisation, therefore only 49 practices (49% of the total) randomised any children. *Table 6* gives the breakdown of practice and patient recruitment in the UK by trust.

Table 7 details the characteristics of the GP practices in which the RNs were based. Some RNs worked as practice nurses fitting the study around their other duties, others were solely employed to conduct research in their practice and generally worked part-time unless they were participating in many studies.

Recruitment of children

Recruitment of children took place from January 2004 until April 2007. From January 2004 to April 2005 AM was part of the study, from May 2005 onwards it was removed. In the part of the study with AM, 55 practices invited 1292 children of which 1236 (96%) were screened. The children who failed at this point ($n = 281$, 23%) entered the 3-month period of AM, at the end of which they

TABLE 5 *Recruitment of practices*

Year	Recruited	Total before losses	Lost	Active
2003	32	32	0	32
2004	28	60	6	54
2005	25	79	15	64
2006	14	78	24	54
Total	99		44	

TABLE 6 *Numbers of practices, children screened and recruited by primary care trust area (PCT)*

PCT[a]	Practices recruited	Children attending first appointment	Children recruited
England			
Adur, Arun and Worthing	1	9	1
Barnet	1	10	1
Barnsley	1	4	0
Bolton	2	93	25
Bracknell Forest	1	102	10
Bristol North	2	31	0
Norwich	1	14	0
Broxtowe and Hucknall	1	0	0
Burnely, Pendle and Rossendale	1	20	1
Carlisle and District	2	27	2
Cotswold and Vale	1	19	2
Craven, Harrogate and Rural	1	24	3
Durham Dales	3	108	7
Exeter	5	85	6
East Elmbridge and Mid Surrey	2	25	0
East Hampshire	1	0	0
Eastleigh and Test Valley South	1	8	2
Guildford and Waverley	1	0	0
Haringey Teaching	1	0	0
Herefordshire	3	72	5
Heywood and Middleton	1	5	0
Ipswich	1	60	7
Langbaurgh	1	48	4
Medway	3	12	3
Mendip	2	1	0
Middlesbrough	1	9	0
Morecambe Bay	1	29	0
North and East Cornwall	1	0	0
North Bradford	2	51	6
North Devon	3	192	17
North Hampshire	2	0	0
North Somerset	1	48	11
Northampton	2	46	5
Poole	1	16	4
Redditch and Bromsgrove	2	86	6
Richmond and Twickenham	1	8	0

TABLE 6 *Numbers of practices, children screened and recruited by primary care trust area (PCT) (continued)*

PCT[a]	Practices recruited	Children attending first appointment	Children recruited
Royston, Buntingford and Bishop's Stortford	1	9	0
Scarborough, Whitby and Ryedale	1	3	0
Selby and York	1	44	4
Shropshire County	1	88	10
Solihull	1	24	1
South East Oxfordshire	1	73	9
South Peterborough	1	2	1
South West Kent	1	19	3
South West Oxfordshire	1	64	3
South Worcestershire	2	159	9
Vale of Aylesbury	1	10	2
Walsall	3	25	1
Warrington	1	0	0
Waveney	1	1	1
West Lancashire	1	0	0
West Wiltshire	1	0	0
Windsor, Ascot and Maidenhead	3	5	0
Woking	1	1	0
Wyre Forest	2	31	4
Northern Ireland[b]	4	91	12
Scotland			
Borders Health Board	1	30	4
Fife NHS Board	3	27	6
Forth Valley	1	3	0
Grampian Local Health Board	1	33	0
Greater Glasgow	1	0	0
Highland Health Board	1	26	2
NHS Tayside	1	33	0
Wales			
Cardiff	1	0	0
Pembrokeshire Local Health Board	2	79	11
Powys Local Health Board	1	48	6

a Owing to NHS trust restructuring, some of these trusts may have merged or changed their names.
b No PCTs in Northern Ireland.

TABLE 7 *Practice characteristics*

			UK
Practice list size	Mean (range)	9362 (2400–20 to300)	6093
Number of partners	Mean (range)	5 (1–10)	4
Practice country	England	83 (83.8)	8542[a]
	Scotland	8 (8.1)	1056[a]
	Wales	4 (4)	501[a]
	Northern Ireland	4 (4)	366[a]
Practice location	Cities	9 (9.1)	
	Industrial	13 (13.1)	
	Inner London	1 (1)	
	Outer London	2 (2)	
	Other metropolitan districts	10 (10.1)	
	Mixed urban rural	25 (25.3)	
	Remote rural	17 (17.2)	
	Resort/Sea/Retired	4 (4)	
	With new towns	5 (5.1)	
	Not known	13 (13.1)	
Carstairs deprivation score	Mean (range)	0.275 (–5.36 to 21.73)[b]	0 (–5.71 to 16.50)[99]

Figures are *n* (%) unless otherwise stated.
a Total number of GP practices by country from Key Demographic Statistics from UK General Practice using 2004 data.[98]
b From 1991 Census.

were screened again and those still failing were eligible to be randomised ($n = 87$, 31%). When AM had been removed from the methodology, 54 practices invited 898 children of which 96% were screened, 174 (20%) failed the tympanometry thus were eligible to be randomised. Two hundred and seventeen children were randomised in total: 72 randomised (83% of those eligible) at 32 practices in the phase with AM and 145 (83% of those eligible) at 38 practices without prior AM.

Figure 3 provides details of screening, randomisation and follow-up in accordance with the CONSORT statement. The CONSORT diagram has been separated into with and without AM up to and including the randomisation point. There is a slight disparity between the two treatment arms with seven more children having been randomised to the placebo treatment than the active one – this was a chance occurrence as all RNs used sprays numbered consecutively (checked by trial audit) and the study remained blinded until follow-up ended and analysis began. This small imbalance is further reduced in follow-up assessments.

Patient characteristics

Screened children

Table 8 details the characteristics of the 2093 children who were screened. The minimum age shown in *Table 8* is 44 months, this was 4 months less than the age at which children could be randomised (i.e. 48 months, 4 years). This lower age was acceptable at screening in children who were in the first part of the study with AM as this was a period of 3 months, and with the difficulties in scheduling assessments, 44 months was the lower limit for inviting children for screening. Eligible children had to be 48 months old (4 years old) at the point of randomisation as per the inclusion criteria.

Table 9 details the baseline characteristics of the 217 children randomised and of their parents (guardians) by the different treatment groups for 13 variables of potential significance as confounders. There were no obvious differences between the two treatment arms of the study other than the ratio of males to females, 1:1 in the active groups and 1:0.8 in the placebo group.

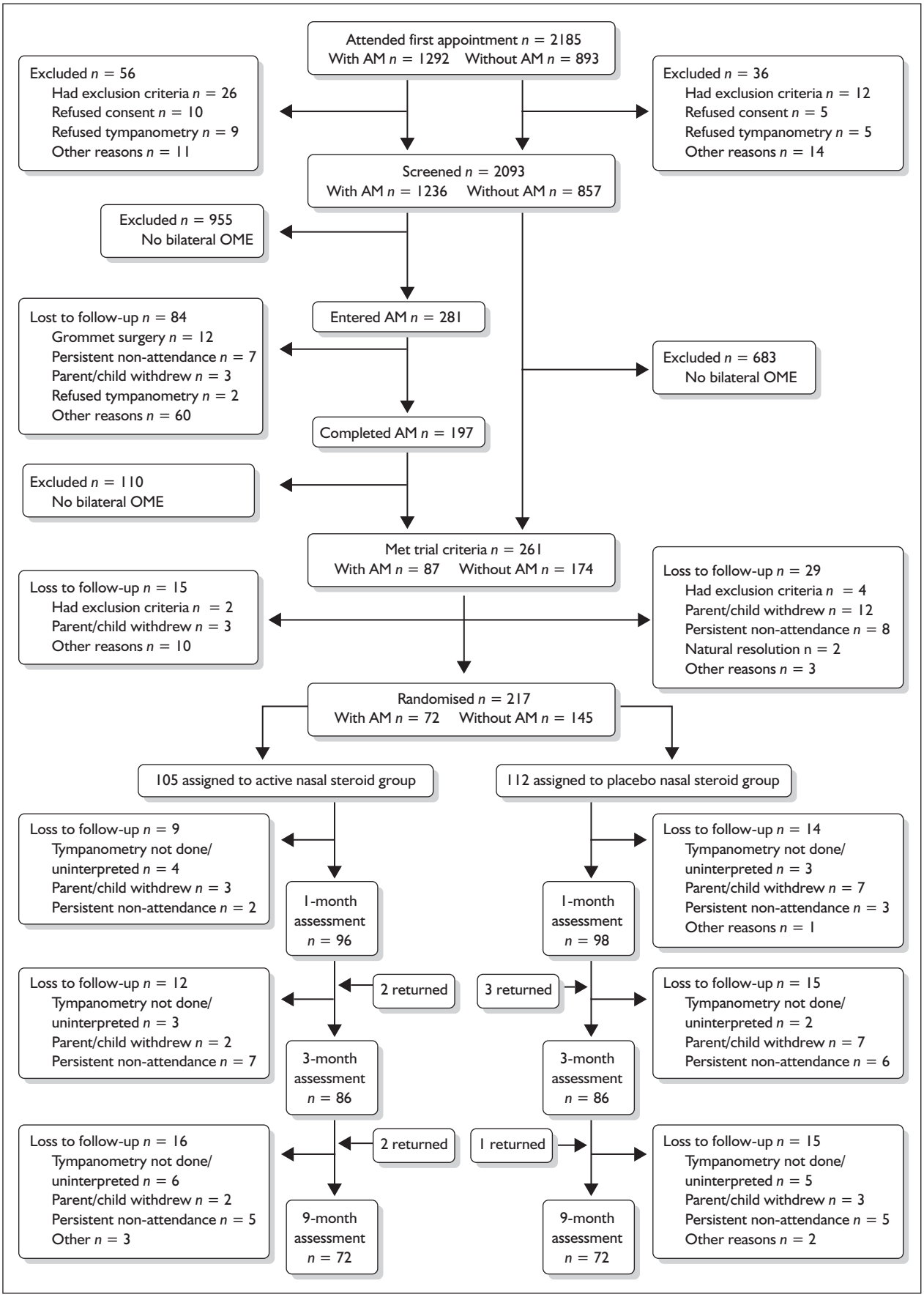

FIGURE 3 *CONSORT diagram.*

TABLE 8 *Characteristics of screened children (n = 2093 unless otherwise stated)*

Age (months)	Mean (SD)	81.3 (24.2)
	Range	44–143
Gender (*n* = 2084)	Male	1046
	Female	1038
Season screened	January–March	925
	April–December	1168
Frequency of GP surgery episodes in the last 12 months for ear-related problems (*n* = 215)	Mean (SD)	1.88 (1.59)
	Range	0–19[a]

a 0 is indicative of a child found through referral from a health-care professional, their past history was not required.

TABLE 9 *Baseline characteristics of randomised children*

		Active (*n* = 105)	**Placebo (*n* = 112)**
Age (months)	Mean (SD)	73.3 (20.2)	72.1 (18.6)
	Range	49–129	48–125
Gender	Male	52 (50)	63 (56)
	Female	53 (50)	49 (44)
Season randomised	January–March	42 (40)	44 (39)
	April–December	63 (60)	68 (61)
Source	Referral	12 (11)	15 (13)
	Computer audit	93 (89)	97 (87)
Daycare (active *n* = 104, placebo *n* = 106)	No	3 (3)	1 (1)
	Yes	101 (97)	105 (99)
Smoking in household (active *n* = 104, placebo *n* = 106)	No	95 (91)	96 (91)
	Yes	9 (9)	10 (9)
Atopy	No	70 (67)	79 (71)
	Yes	35 (33)	33 (29)
Ethnicity (active *n* = 68, placebo *n* = 69)[a]	White	66 (97)	66 (96)
	Bangladeshi/Indian	0 (0)	2 (3)
	Mixed	2 (3)	1 (1)
Age at first ear infection (active *n* = 102, placebo *n* = 106)	Has not had one	0 (0)	1 (1)
	< 12 months	27 (26)	31 (29)
	12–24 months	44 (43)	40 (38)
	2–3 years	14 (14)	16 (15)
	≥3 years	17 (17)	18 (17)
Frequency of GP surgery episodes in last 12 months for ear-related problems (active *n* = 103, placebo *n* = 112)	Mean (SD)	2.29 (1.96)	2.13 (1.53)
	Range	0–14	0–9
Parent reported frequency of ear infections in last 12 months for hearing-related problems (active *n* = 104, placebo *n* = 106)	None	6 (6)	6 (6)
	1–2	35 (34)	50 (47)
	3–4	41 (39)	33 (31)
	≥5	22 (21)	17 (16)

TABLE 9 *Baseline characteristics of randomised children (continued)*

		Active (*n* = 105)	Placebo (*n* = 112)
Grommets inserted > 12 months prior to randomisation (active *n* = 95, placebo *n* = 102)	No	95 (100)	100 (98)
	Yes	0	2 (2)
Adenoidectomy performed prior to randomisation (active *n* = 95, placebo *n* = 102)	No	94 (99)	100 (98)
	Yes	1 (1)	2 (2)
Highest qualification achieved by parent (active *n* = 66, placebo *n* = 70) and second parent (active *n* = 59, placebo *n* = 54)[a]	School to 16, no qualifications	9 (14)	5 (7)
		8 (13)	8 (15)
	School to 16, GCSEs/O-Levels	18 (27)	23 (33)
		26 (44)	19 (35)
	Sixth form school or college, A-Levels, ND	15 (23)	12 (17)
		7 (12)	8 (15)
	Highers, Scotvec or NVQ	11 (17)	16 (23)
		8 (13)	6 (11)
	University degree	10 (15)	10 (14)
		4 (7)	5 (9)
	Professional or postgraduate degree	3 (4)	4 (6)
		6 (10)	8 (15)

Figures are *n* (%) unless otherwise stated.
a Data were collected only after AM was removed.

Data collection and follow-up rates

Timing of follow-up assessments

The follow-up assessments were at 1, 3 and 9 months post baseline; the RNs were instructed to conduct these assessments as close as possible to the time intervals required, subject to the child's availability. All three assessments required some flexibility due to the limited times at which the RNs could see the children (the study age group meant most of the children were at school). Unless an appointment coincided with a school holiday, the only times the RNs could see the study children was from 4 PM onwards. This restricted time frame meant that if an appointment was missed the next convenient or available one could be a week later, thus delaying the assessment. *Table 10* provides the timings of each follow-up assessment.

Table 11 shows the data that were available at each assessment from baseline onwards. Ninety-three per cent of children returned for their 1-month follow-up, 83% for their 3-month visit and 75% for their 9-month follow-up assessment. These figures are not shown in the CONSORT diagram (see *Figure 3*) as this uses follow-up figures related to the main outcome measure of the study, i.e. the tympanometry measuring presence of ear effusions at 1, 3 and 9 months post baseline, therefore the CONSORT percentages for follow-up, 89%, 79% and 66% respectively, are based upon numbers of children having tympanometry performed at each visit.

Exclusions and losses to follow-up

Children who were not screened having attended their first appointment [56 (4%) with AM and 36 (4%) without AM] mainly possessed an exclusion criterion or did not have all the inclusion criteria. *Table 12* lists the reasons for exclusion at this stage.

Of the 281 children who entered AM, 84 (30%) were lost to follow-up, i.e. they did not return at the end of the 3-month period. *Figure 3* details the reasons for the loss at this stage. The majority of these (*n* = 49, 82% in the 'Other' category of *Figure 3* for this stage) were due to the break in trial spray supplies by Schering-Plough. This break in supply meant that if children did return, and were screened and failed (thus eligible) they could not be

TABLE 10 *Timing of assessments*

	Baseline to 1 month	Baseline to 3 months	Baseline to 9 months
n	202	181	162
Mean (SD) days from baseline	32.87 (8.77)	93.93 (17.43)	278.25 (27.12)

TABLE 11 *Data availability at each time point*

	Baseline	1 month	3 months	9 months
Measures performed by RN				
Tympanometry	217 (100)	194 (89)	172 (79)	144 (66)
Audiometry	203 (94)	196 (90)	181 (83)	151 (70)
Parent/child reported				
Costs to parents form	213 (98)[b]	–	119[a] (55)	157 (72)[b]
OM8-30	197 (91)	–	175 (81)	160 (74)
EQ-5D	137[a] (63)	–	118[a] (54)	115[a] (53)
HUI	139[a] (64)	–	118[a] (54)	118[a] (54)
Diary	–	197 (91)	170 (78)	–
RN recorded				
Adherence form	204 (94)	172 (79)	–	–
Health economics evaluation form	216 (99)[b]	–	–	200 (92)[b]
Exit interview	–	–	–	157 (72)
Children attending assessment	217	202	181	162
% retention		93	83	75

Figures are *n* (%).
–, not performed.
a Only used after AM had been removed.
b Contains different versions for with and without AM.

randomised as there was no trial medication. It was decided not to bring these children back at their allotted time, and the parents (guardians) were notified of the situation and offered a screening that would not be part of the trial. When the trial medication supply was recommenced, these children were rescreened and entered into AM if they failed the tympanometry. However, a review of the protocol (version 2, dated 16 June 2004) took place and AM was removed from the methodology (version 3, dated 5 May 2005) during the break in medication supply. Many of these children who were effectively 'stuck in AM' were reinvited in the autumn of 2005 for rescreening and, if eligible, they were randomised into the trial, now without AM. Therefore, most of these children were not lost from the study, they were assigned a new study number (NB: a previously randomised child could not be reinvited into the study).

Two hundred and sixty-one children in total were eligible for randomisation, 15 of the 87 (17%) with AM and 29 of the 174 (17%) without AM were lost at this stage. *Figure 3* details the reasons for these 44 children not being randomised. The 'Other' category in the AM group, $n = 10$, consisted of scheduled appointments that coincided with notification of the break in trial medication supply

TABLE 12 *Reasons for children not being screened after attending the first appointment (with and without AM)*

	With AM	Without AM
Exclusions		
Grommet	15	7
Listed for grommets	4	0
Growth concerns	1	1
Hypersensitive to mometasone	0	1
Too young	6	3
Refused consent	10	5
Refused tympanometry	9	5
Other		
Perforation		1
No data	11	3
Wax		9
Foreign body present		1
TOTAL	56	36

(children were screened as they entered the surgery for their appointments), as did the without AM group, $n = 3$.

The losses to follow-up post randomisation are given in *Figure 3* for the active and placebo groups. Persistent non-attendance (all RNs followed the same procedure from their handbook for non-attendees, the child was considered lost to follow-up only after two telephone calls and one recorded delivery reminder to the parents) did not differ between the two groups. New losses to follow-up did not increase over time with each successive follow-up assessment as may be expected but peaked at the 3-month assessment (at 1 month 22% of total losses were non-attendees, 48% at 3 months and 32% at 9 months). Parent/child choice withdrawals in total decreased over time (1 month 43%, 3 months 33% and 9 months 16%); however, there were over twice as many withdrawals of this kind in the placebo group overall compared with the active treatment group ($n = 17$, 39% versus $n = 7$, 19%). Non-interpretable tympanometry was consistent across the assessments with $n = 4$; however, tympanometry not done, which was due to the presence of grommets, was variable with three children at 1 month, one child at 3 months and seven children at 9 months. As expected, more children had had grommets by the 9-month assessment as, by taking part in the study, a potential hearing problem had been highlighted to the parents/GPs, and therefore referral was more likely.

Chapter 4
Results

Main findings

Clinical outcomes

Of the pre-specified potential effect modifiers in the protocol analysis plan [age continuous variable $p = 0.93$; season (school spring term January–March versus other months dichotomous) $p = 0.69$; atopy (any history of asthma, eczema, hay fever/allergic rhinitis versus none) $p = 0.61$; and clinical severity score (defined as the first principal component – accounting for 24.6% of the variance with an Eigen value of 1.38 – of the following baseline variables: frequency of surgery attendance in last 12 months for ear-related problems; total parent-reported episodes of ear problems over last 12 months; age of first episode of hearing infection/problem; tympanogram readings; OM8-30 RESP score (adenoidal factor) $p = 0.006$], only clinical severity had an effect on outcome (*Table 13*). These variables were used in the logistic regression to derive AORs for the main outcomes.

Interaction tests were then carried out between randomisation group and each of age, season, atopy and clinical severity score – defined as above (*Table 14*).

Three models containing the interactions listed in *Table 14* (Models 2, 3 and 4) were compared with Model 1 (containing no interaction) using the likelihood ratio test. The likelihood ratio statistic was compared with a chi-squared distribution with 1 df, whose critical value to reach significance at the 5% level is 3.841. It can be seen from *Table 14* that none of the interactions included in Models 2, 3 and 4 reached significance at the 5% level.

The main outcome was based at 1 month and, using objective tympanometric criteria for children cured, the AOR of 0.93 (95% CI 0.50 to 1.75) favoured placebo treatment (*Table 15* and *Figure 4*). The 95% CIs include an OR of 1 and so were not statistically significant. The risk reduction of the treated group calculated at 1 month was –4.3% (95% CI –18.95% to 9.26%). The effect size using the upper 95% confidence limit therefore is not likely to contain a clinically useful effect, i.e. be less than an NNT of 11 for a 1-month course of treatment.

Thus nasal steroids are very likely to be clinically ineffective because they are no better than placebo in producing resolution of middle ear effusions at 1 month, and also have non-significant secondary outcome efficacy in clearing effusions at 3 months (see *Table 15* and *Figure 4*) and demonstrate no longer term efficacy at 9 months (see *Table 15* and *Figure 4*).

A sensitivity analysis was performed because some children in this study received AM for 3 additional months. When the inclusion criteria of previous history and bilateral fail criteria on two occasions 3 months apart were changed later in the trial to previous history and a bilateral fail on one occasion (i.e. without the addition of AM), a sensitivity analysis was required, which found that there was no significant difference in cure rates whether children were in the AM group or not. It can be seen that there was no significant difference between the odds of cure for the two groups (with and without AM), as the CIs overlap (*Table 16*).

TABLE 13 *Logistic regression with adjustment for four covariates and treatment group*

	p-value	Odds ratio (95% CI)
Treatment group	0.831	0.934 (0.498 to 1.751)
Season	0.695	1.136 (0.600 to 2.151)
Age	0.935	0.999 (0.983 to 1.016)
Atopy	0.608	0.839 (0.428 to 1.642)
Clinical severity score	0.006	1.649 (1.154 to 2.357)

TABLE 14 *Results for interaction tests*

Model	Outcome	Explanatory variables	–2 log likelihood	Likelihood ratio	Statistical significance
1	Pass/Fail at 1 month	Treatment group, season, age, clinical severity	222.316	NA	NA
2	Pass/Fail at 1 month	As Model 1 plus age by treatment group interaction	221.922	0.394	No
3	Pass/Fail at 1 month	As Model 1 plus atopy by treatment group interaction	220.843	1.473	No
4	Pass/Fail at 1 month	As Model 1 plus clinical severity by treatment group interaction	222.298	0.018	No

TABLE 15 *Children cured of OME using tympanometric criteria (i.e. proportions of children with either A or C1 tympanogram in ≥ 1 ear)*

	Active	Placebo	Unadjusted OR (95% CI)	AOR (95% CI)
Cured at 1 month	39/96 (40.6)	44/98 (44.9)	0.84 (0.475 to 1.484)	0.934 (0.498 to 1.751)
Cured at 3 months	50/86 (58.1)	45/86 (52.3)	1.265 (0.693 to 2.311)	1.451 (0.742 to 2.838)
Cured at 9 months	40/72 (55.6)	47/72 (65.3)	0.665 (0.34 to 1.302)	0.822 (0.387 to 1.746)

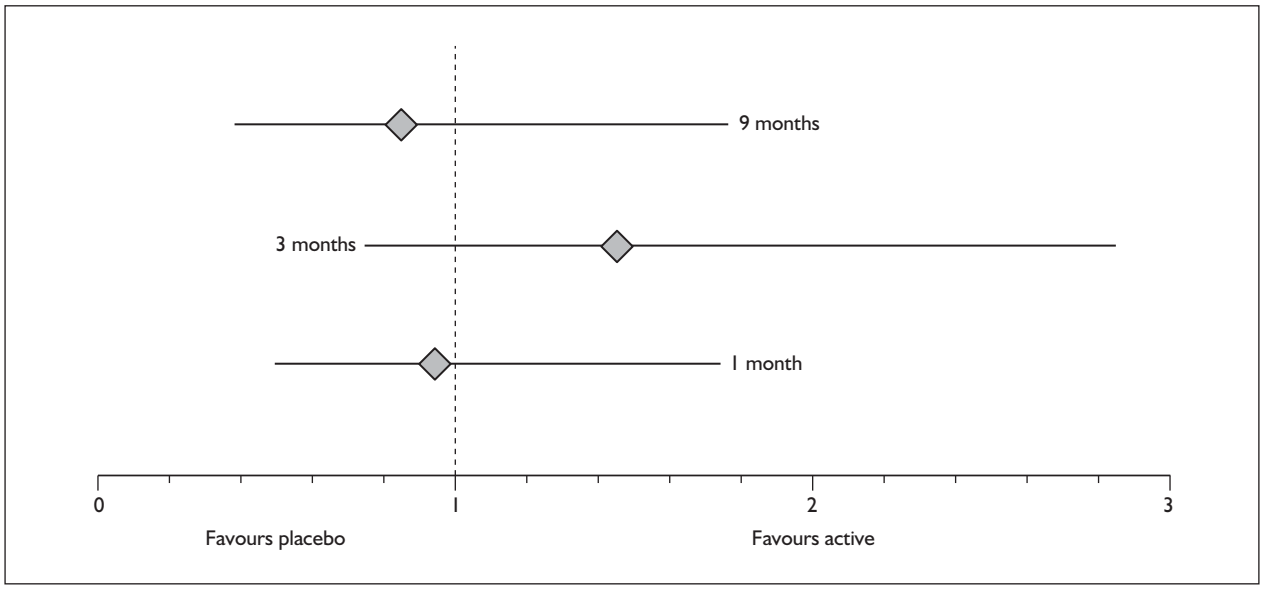

FIGURE 4 *AORs with 95% CI for active versus placebo comparative efficacy at 1, 3 and 9 months post baseline.*

Testing for an association between AM and tympanometry pass rate at 1 month using a chi-squared test did not give a significant association in the placebo group ($p = 0.726$) or in the active group ($p = 0.378$). Similarly, testing for an association between AM and tympanometry pass rate at 3 months using a chi-squared test did not give a significant association in the placebo group ($p = 0.143$) or in the active group ($p = 0.186$). These findings support the view that topical steroids are inefficacious even in the more persistent cases as defined by tympanometry fails on two occasions 3 months apart (one definition of severity).

TABLE 16 *Sensitivity analysis +/– AM on outcomes at 1 and 3 months post baseline*

		Active	Placebo	OR (95% CI)
1 month	AM	11/32 (34.4)	14/33 (42.4)	0.71 (0.26 to 1.94)
	No AM	28/64 (43.8)	30/65 (46.2)	0.91 (0.45 to 1.82)
3 months	AM	14/29 (48.3)	10/25 (40)	1.40 (0.47 to 4.13)
	No AM	36/57 (63.2)	35/61 (57.4)	1.27 (0.61 to 2.67)

The method of study entry, either by computer audit (c) or in-house referral at presentation (i) did not effect tympanometric outcomes. At 1 month 58% (c) versus 55% (i) were not cured; at 3 months 45% (c) versus 43% (i); and at 9 months 40% (c) versus 33% (i).

Effectiveness outcomes

The OM8-30 measure, developed by the MRC, showed equally null results for this important secondary outcome at 3 and 9 months. The main outcomes presented are median scores with interquartile ranges (IQRs) based on scales developed by the MRC for use with this questionnaire: a total score (p-values at baseline, 3 months, 9 months; $p = 0.33$, $p = 0.55$, $p = 0.77$ respectively) (*Figure 5*); DEV ($p = 0.94$, $p = 0.83$, $p = 0.24$) (*Figure 6*); RESP (adenoidal factor) ($p = 0.83$, $p = 0.22$, $p = 0.17$) (*Figure 7*); PHYS ($p = 0.41$, $p = 0.91$, $p = 0.69$) (*Figure 8*); and RHD ($p = 0.32$, $p = 0.08$, $p = 0.47$) (*Figure 9*).

In the following figures, missing data resulted in low analysis rates for the specific questionnaire-derived scores because of validity issues. Those presented required complete data for every question on the 30-item questionnaire. The box plots present the median and IQR and the vertical lines show the range unless the point is considered to be an outlier as determined by SPSS version 12.0. (The definition of an outlier in this statistical package is 1.5 times the IQR.)

All these scales, despite the probability of a false positive outcome, showed non-significant differences between groups. What was also clearly apparent from the figures was a consistent recovery process by 3 months with little further gain by 9 months. While the MRC measure is currently widely validated as part of the Eurotitis study, its validity against a QoL measure is yet to be fully determined. Nonetheless, as a disease-specific functional health status measure it is likely to be the most sensitive and responsive psychometric measure currently available to evaluate impact of OME on a child's symptoms and life. The sample size analysed would be expected to detect 0.5 SD effect on the scales, which would be clinically important. The null findings of effectiveness found here reinforce further the null tympanometric efficacy findings between active and placebo arms.

Four measures of hearing were used in this study: two subjective, the reported HL scale on the OM8-30 (see *Figure 9*) and days with reported hearing loss on the prospective child's 3-month diaries (Mann–Whitney test for prospectively recorded data in 3-month diaries showed no significant differences between groups, $p = 0.45$ for days with suspected hearing loss); and two objective, pass fail on sweep hand-held audiometers at 25 dB HL (fail on more than two frequencies both ears at 0.5, 1, 2, 3, 4 kHz) (*Figure 10*) and the audiometrically validated scale ACET, a continuous severity scale for middle ear function (*Figure 11*). None of these outcomes, although improving over time, showed any significant differences between groups (*Table 17*).

A Spearman correlation showed a moderate correlation between the two subjective measures (the reported HL scale on the OM8-30 and days with reported hearing loss from the 3-month diaries) ($r = 0.567$, $p < 0.001$).

Days with otalgia or earache were considered an important secondary outcome for which 3-month prospective diary information was collected and also retrospectively measured on the OM8-30. Days with otalgia were not significantly different between treatment groups at 1 month [$p = 0.43$; median (IQR): placebo = 0 (0–2.25), active = 0 (0–3)] nor at 3 months [$p = 0.46$; median, IQR: placebo = 1 (0–4), active = 1.5 (0–5)].

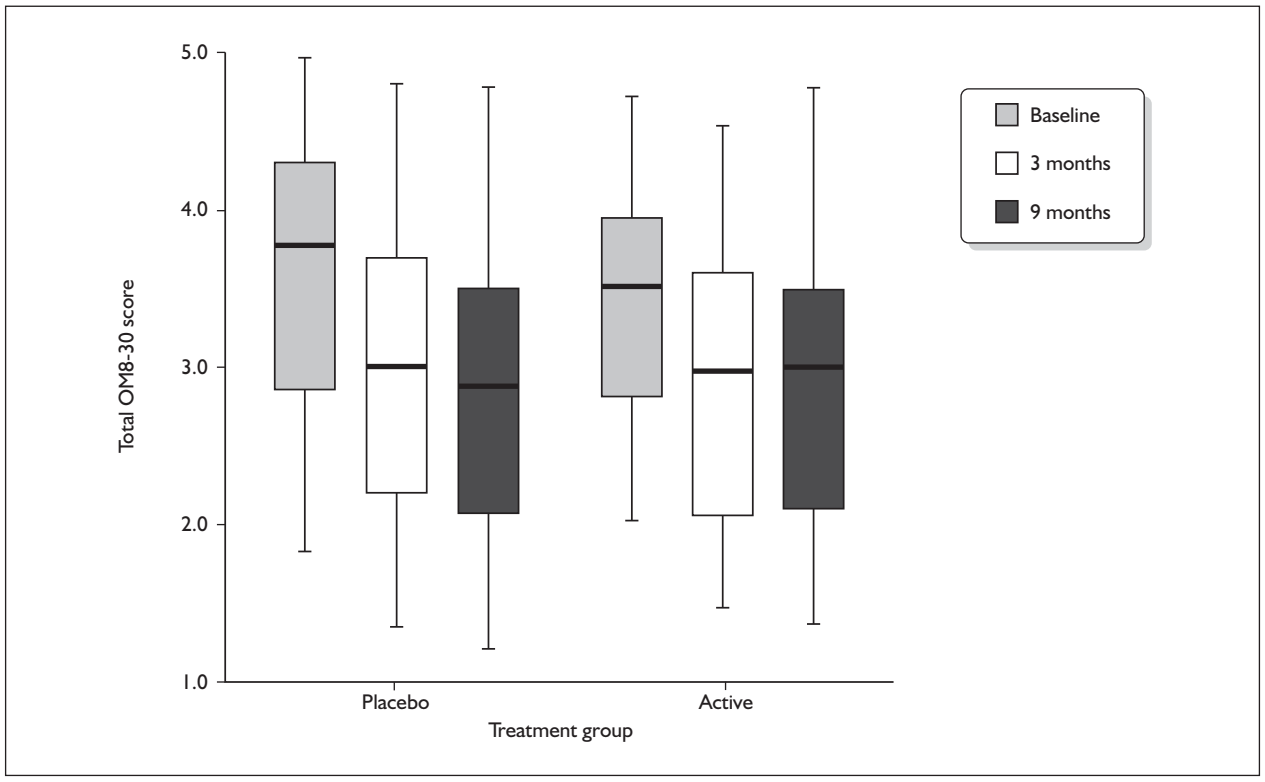

FIGURE 5 *Box plots of total OM8-30 score at baseline, 3 months and 9 months showing median and IQR by treatment group (*n *= 39 in active group and* n *= 43 in placebo group at baseline, 3 and 9 months).*

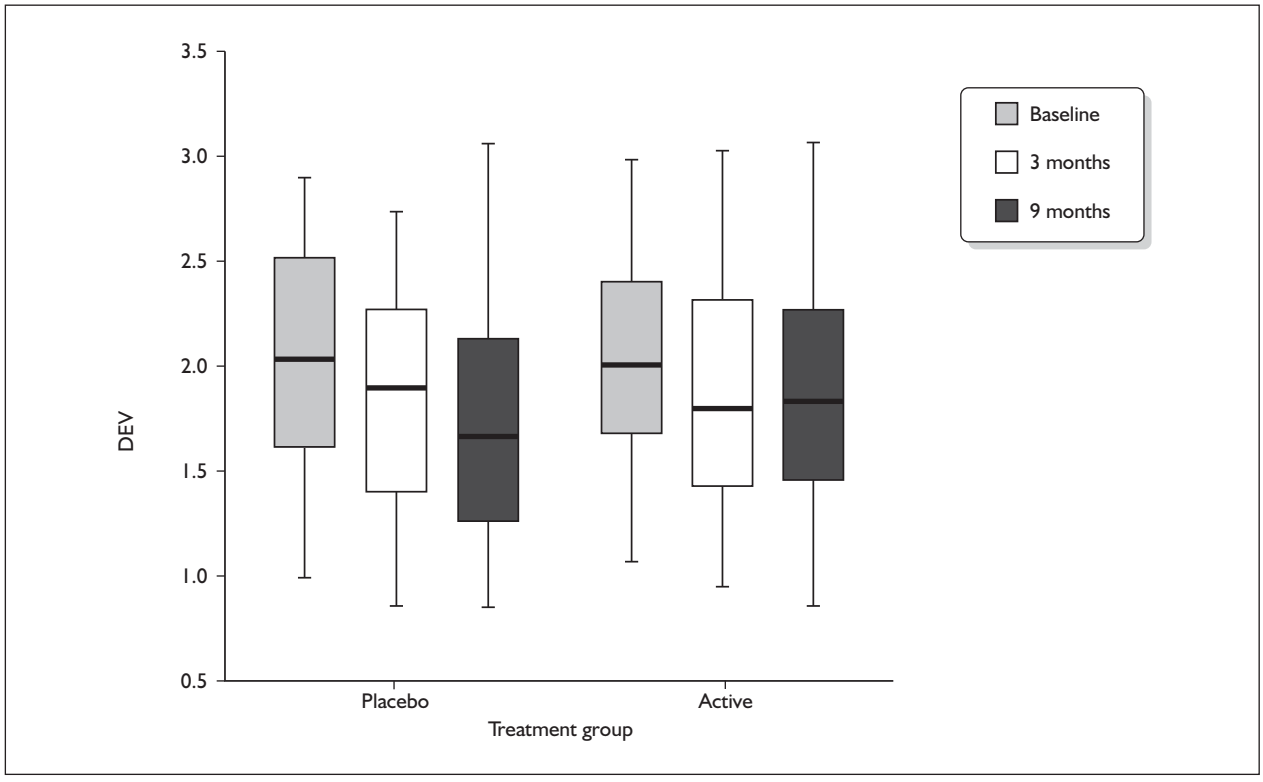

FIGURE 6 *Box plots of DEV at baseline, 3 months and 9 months showing median and IQR by treatment group (*n *= 48 in active group and* n *= 55 in placebo group at baseline, 3 and 9 months).*

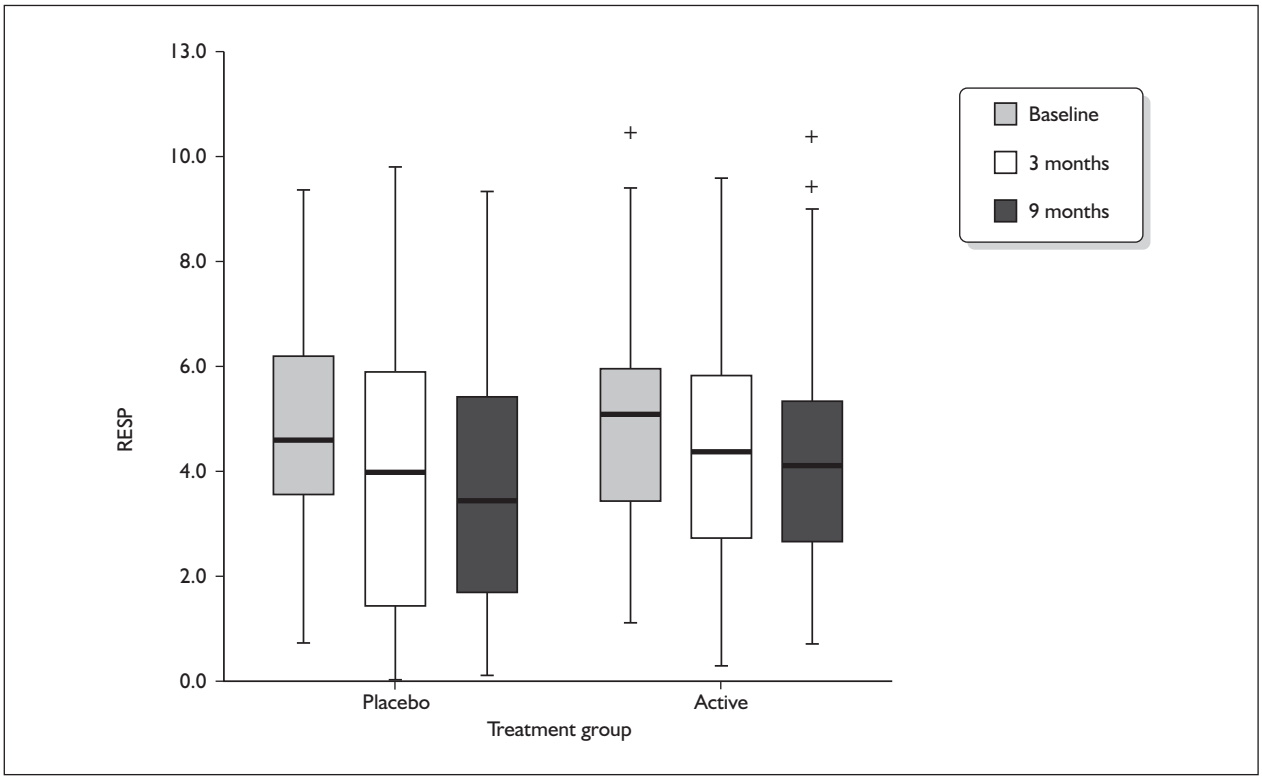

FIGURE 7 *Box plots of RESP at baseline, 3 months and 9 months showing median and IQR by treatment group (*n *= 68 in active group and* n *= 66 in placebo group at baseline, 3 and 9 months). + indicates outliers.*

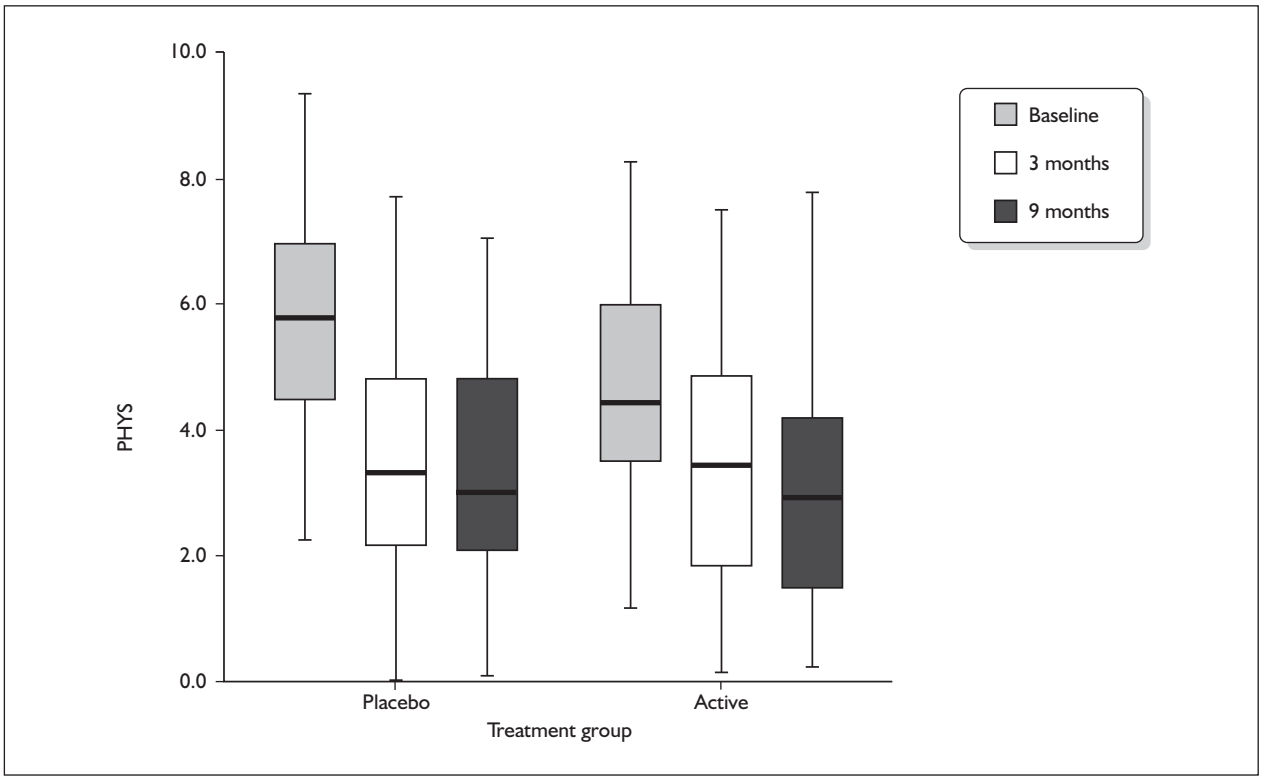

FIGURE 8 *Box plots of PHYS at baseline, 3 months and 9 months showing median and IQR by treatment group (*n *= 58 in active group and* n *= 53 in placebo group at baseline, 3 and 9 months).*

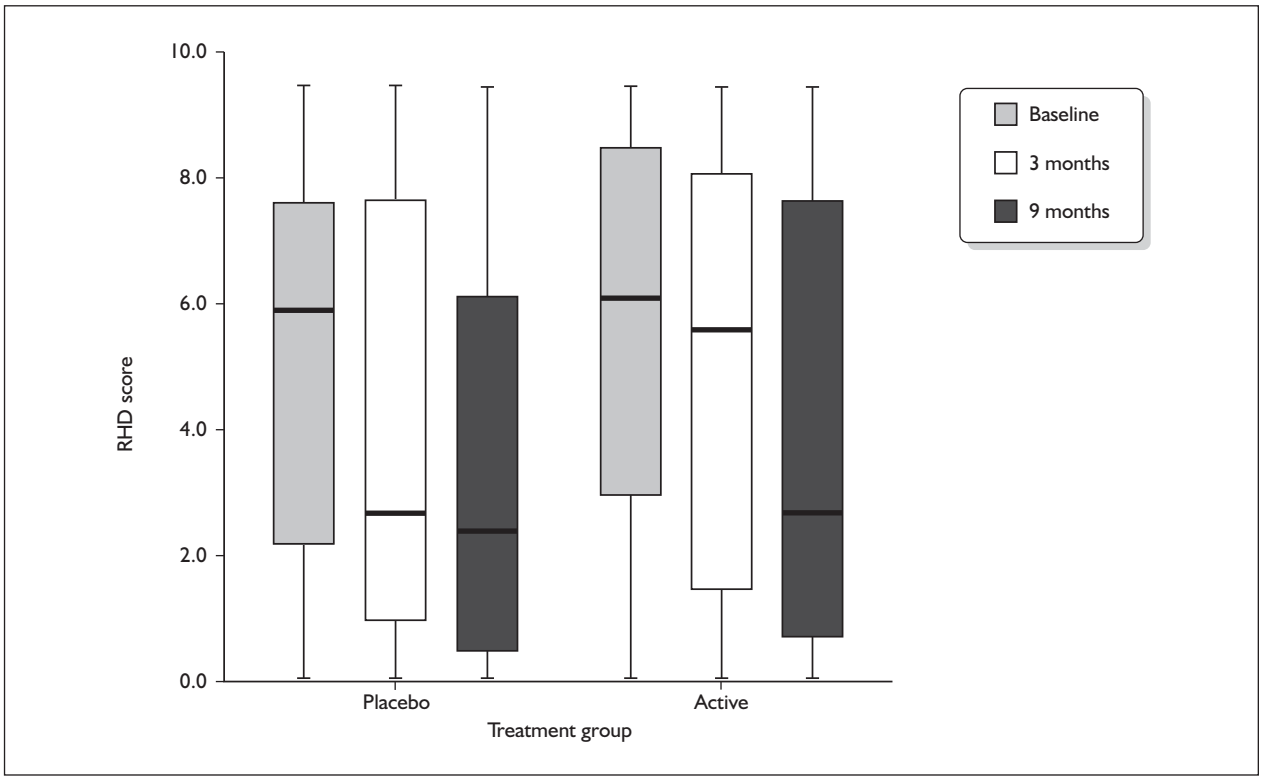

FIGURE 9 *Box plots of RHD at baseline, 3 months and 9 months showing median and IQR by treatment group (*n = *69 in active and placebo groups at baseline, 3 and 9 months).*

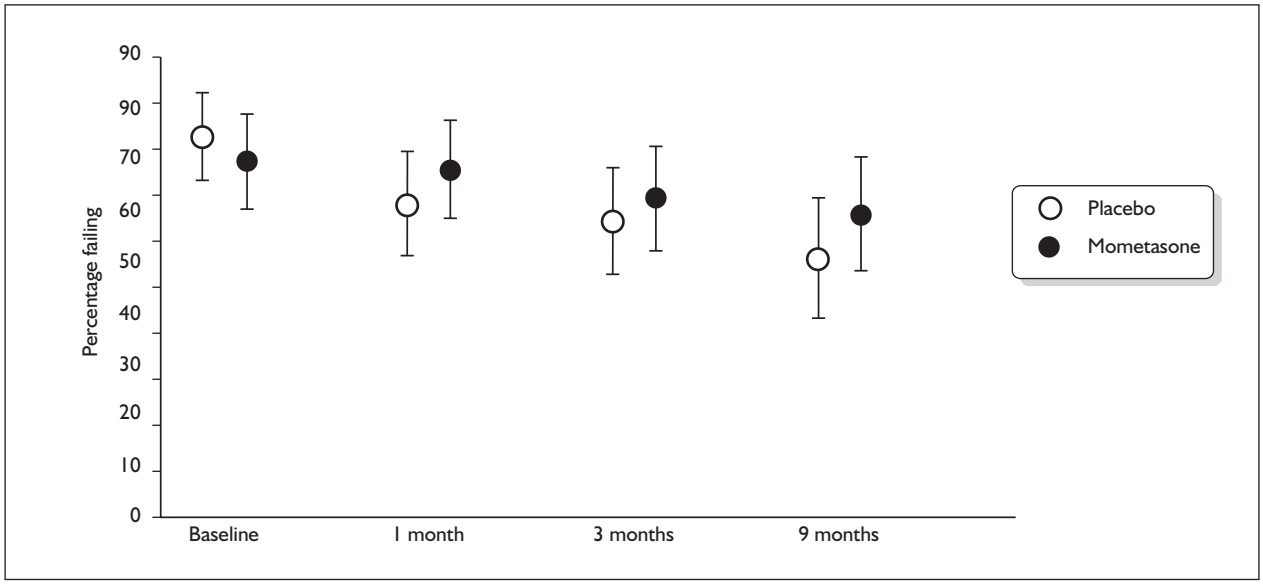

FIGURE 10 *Percentage of children failing audiometry at baseline, 1, 3 and 9 months (±95% CI).*

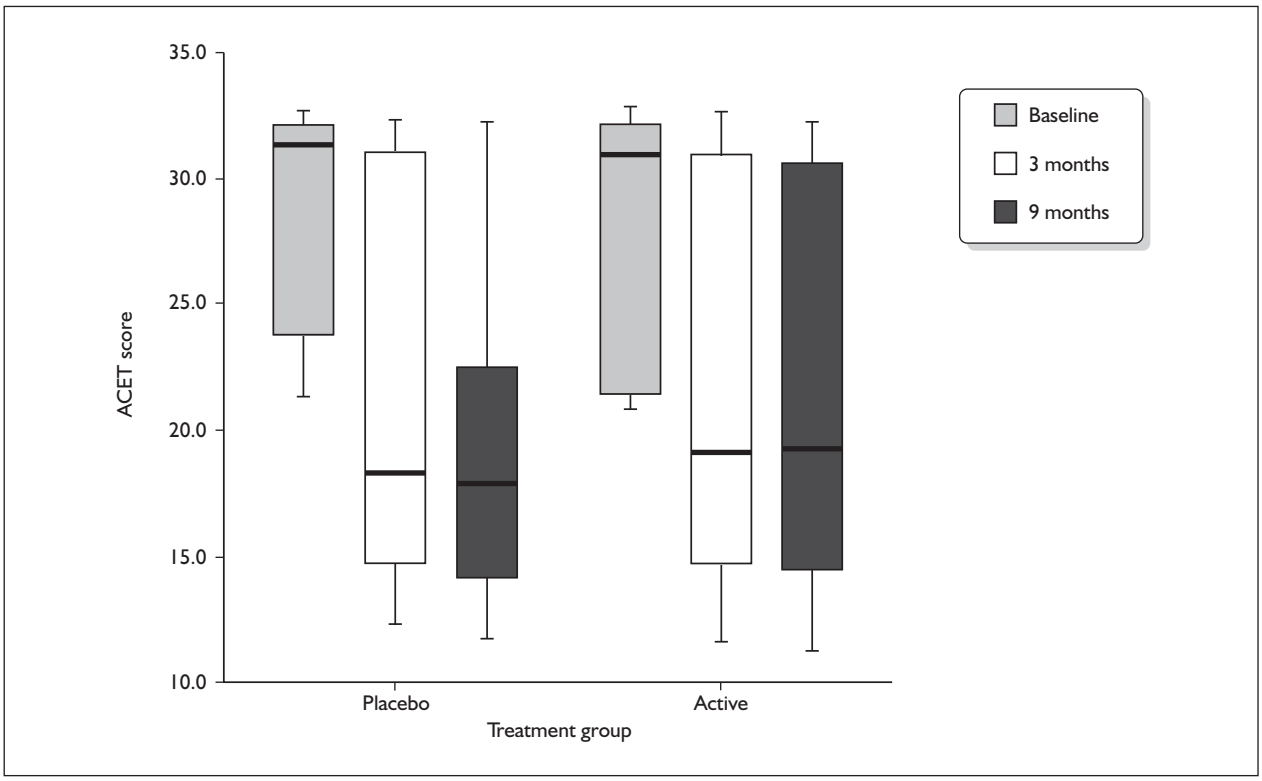

FIGURE 11 *Box plots of ACET at baseline, 3 months and 9 months showing median and IQR by treatment group (*n = *53 in active group and* n = *57 in placebo group at baseline, 3 and 9 months).*

TABLE 17 *Hearing loss: a comparison between groups of the four study measures over time*

	Baseline		3 months		9 months	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Audiometry, % failing	69.6, *n* = 92	74.5, *n* = 98	62.7, *n* = 83	58.0, *n* = 81	59.5, *n* = 74	50.7, *n* = 67
Hearing loss from tympanograms, median (IQR)	30.97 (23.8 to 32.65), *n* = 84	30.94 (24.03 to 2.21), *n* = 96	19.43 (14.64 to 1.21), *n* = 75	21.15 (14.86 to 0.94), *n* = 72	19.56 (14.88 to 0.84), *n* = 61	17.89 (14.11 to 3.55), *n* = 65
Reported hearing difficulties, median (IQR)	6.06 (2.83 to 8.57), *n* = 94	5.88 (2.33 to 7.60) *n* = 102	5.54 (0.90 to 8.43), *n* = 88	3.92 (0.90 to 7.60), *n* = 83	2.33 (0.21 to 7.60), *n* = 79	2.33 (0.42 to 6.60), *n* = 76
Days with hearing loss, median (IQR)			4 (0 to 24.5), *n* = 100	4 (0 to 18.5), *n* = 100		

Adverse events/side effects

Adverse events/side effects are presented in *Table 18*. In total, 45 children (45/96, 46.9%) in the treatment group and 35 (35/98, 35.7%) in the placebo group reported side effects at 1 month, and 29 (29/86, 33.7%) and 23 (23/86, 26.7%) respectively at 3 months. No serious adverse events, suspected serious adverse reactions or related hospitalisations occurred during the study. At 3 months more side effects were reported from use of the active sprays particularly in relation to nosebleeds, dry throat and cough. Side effects were relatively minor but may have affected a child's QoL.

Adherence

Reported adherence data are presented in *Table 19*. At 1 month the reported adherence was 96% for the active treatment and 90% for the placebo, and 88% active and 88% placebo at 3 months (good compliance was considered to be when the parent reported the child as having taken the spray most or all of the time, see *Table 19*). A structured support adherence questionnaire was used to improve reporting (Appendices 6 and 7).

The weights of the returned spray bottles were compared with the reported adherence data. *Figures 12* and *13* show the relationships between the amounts of spray used and the reported usage. The percentage compliance was in excess of 100% for some children, most likely because the nasal applicator on the sprays had a tendency to become blocked and required cleaning. Following such a procedure the RNs were instructed to tell the parents (guardians) that they must reprime the spray (seven actuations). The predicted used weight denominator was determined as an initial priming and one spray per nostril per day for either 28 days (baseline to 1-month assessment) or 56 days (1-month to 3-month assessment), no prediction was made for numbers of times the device may have required cleaning and therefore repriming. The other reason for more than 100% use could be a non-compliance issue with the spray being wasted to mimic adherence. However, the scatter plots (see *Figures 12* and *13*) show a positive relationship between the compliance determined by spray weight used and the reported usage, suggesting that on the whole the sprays were used correctly. No statistics were performed on these data as this was not in the protocol (version 3, dated 5 May 2005).

Concealment

Concealment was evaluated by asking the parents (guardians) to report whether they thought their child was taking active or placebo spray at 7 days post baseline and 7 days post the 1-month assessment (i.e. approximately 35 days post baseline) (see Appendices 6 and 7). The percentage correct guesses were no better than chance alone (*Table 20*). However, most parents (guardians) thought their children were receiving active treatment (83.5% at 7 days post baseline and 65.2% 7 days post 1-month assessment); this demonstrates that blinding for the study was satisfactory with good concealment but confirms the placebo effect (bias) in the study.

TABLE 18 *Side effects experienced while taking active or placebo spray as reported at the 1- and 3-month assessments*

	1-month assessment		3-month assessment	
	Active	**Placebo**	**Active**	**Placebo**
Overall				
Children	43 (55)	35 (45)	29 (56)	23 (44)
Side effects	53 (51)	50 (49)	48 (59)	33 (41)
Individual side effects				
Stinging in the nose	9 (47)	10 (53)	9 (50)	9 (50)
Nosebleed	8 (53)	7 (47)	10 (63)	6 (37)
Dry throat	13 (48)	14 (52)	10 (59)	7 (41)
Cough	23 (55)	19 (45)	19 (63)	11 (37)

Figures are *n* (%).

TABLE 19 *Reported adherence (numbers of children) at the 1- and 3-month assessments*

		Active	Placebo
1 month (active $n = 103$, placebo $n = 99$)	Not at all	1	2
	Some of the time	3	8
	Most of the time	48	36
	All of the time	47	57
3 months (active $n = 90$, placebo $n = 89$)	Not at all	3	3
	Some of the time	8	8
	Most of the time	45	40
	All of the time	34	38

Referrals

Overall, few referrals were made, 32 (taken from health-care usage audits carried out at 9-month assessment, see Appendices 6, 9 and 12) out of 217 or 14.7% over 9-month follow-up, 15 in the active group and 17 in the placebo group. This number was lower than anticipated and may reflect the introduction of AM, a new treatment most parents (guardians) thought was active, or a Hawthorn effect, or all three.

Subgroup analyses

Clinical severity score

This score appeared to be normally distributed and therefore *t*-tests were used to test between groups. A higher baseline clinical severity score meant that the child had a more severe condition. There was a significant difference in baseline clinical severity score between children who passed and failed tympanometry at 1 month ($p = 0.004$).

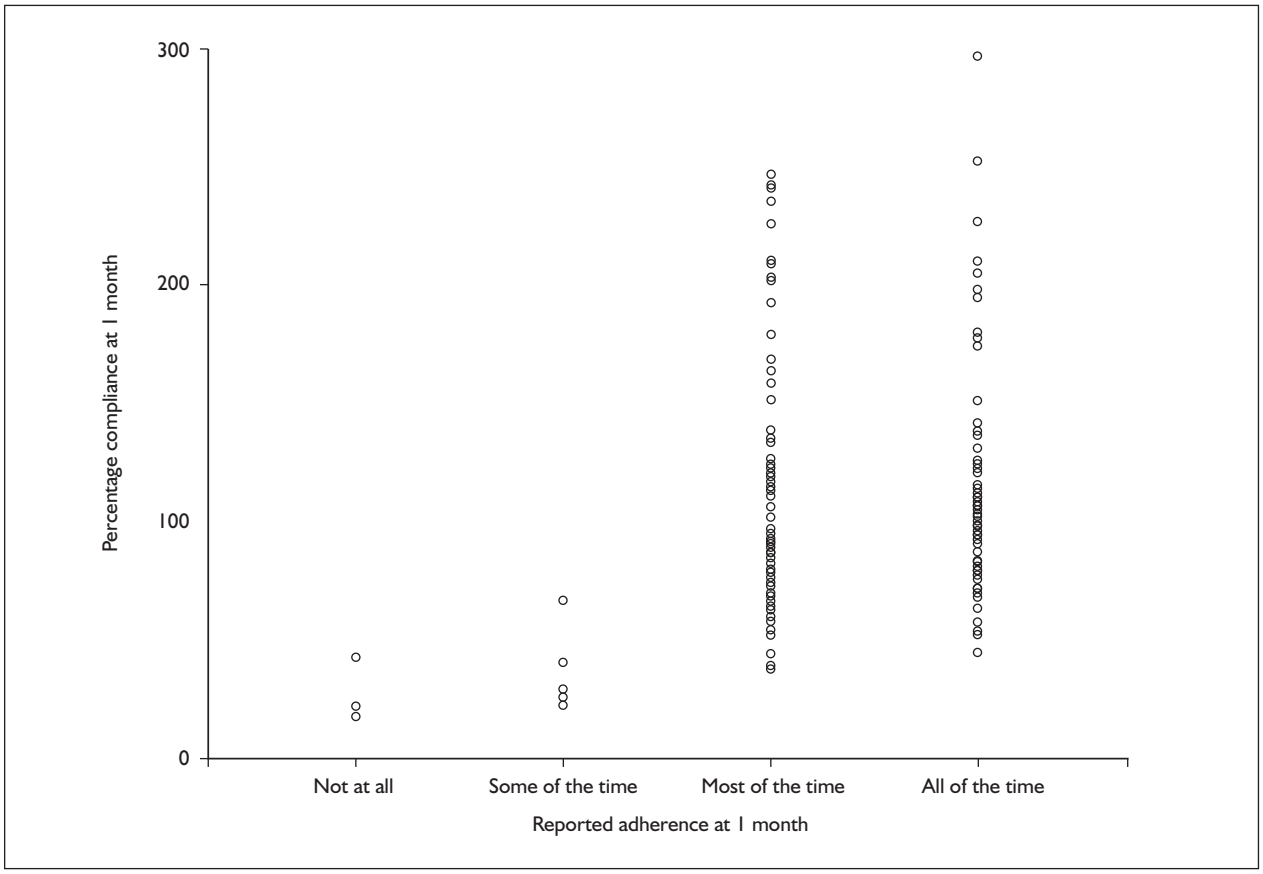

FIGURE 12 *Percentage compliance from the spray bottle weights vs the reported adherence from parents (guardians) at 1 month.*

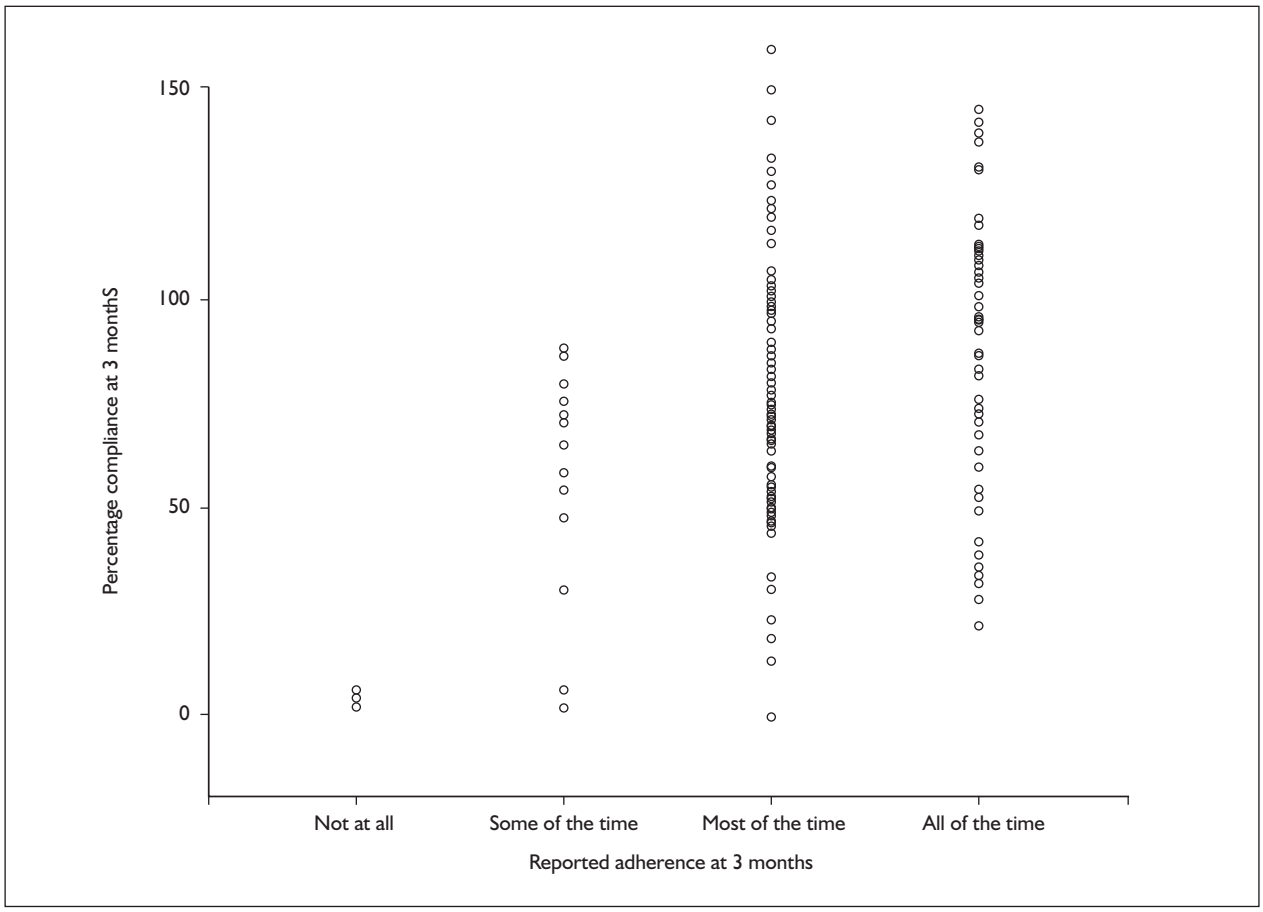

FIGURE 13 *Percentage compliance from the spray bottle weights vs the reported adherence from parents (guardians) at 3 months.*

This result was expected from the outcome of the logistic regression, which was a better method of analysis as it corrected for other factors such as age (as a continuous variable), treatment group and atopy in the model (see Clinical outcomes). There was no significant difference in baseline clinical severity score between children in the different treatment groups ($p = 0.128$).

Clinical severity score and age group

There was a significant difference in baseline clinical severity score between children in the different age groups (4–6.49 years and 6.5+ years) ($p = 0.023$). *Table 21* describes the two age groups in terms of the clinical severity score. The children in the 6.5+ years age group are significantly less severe at baseline.

Age group and tympanometric cure outcomes

Risk estimates are presented as ORs with the 95% CIs for tympanometric cure at 1, 3 and 9 months by age group (*Table 22*). Although there appeared to be a significant OR for treatment of older children at 3 months, the 95% CIs for the

TABLE 20 *Concealment at 7 days post baseline and 7 days post 1-month assessment, percentage of correct guesses by parents (guardians)*

	Active	Placebo
7 days post baseline	47%	53%
7 days post 1-month assessment	49.4%	50.6%

TABLE 21 *Clinical severity score for the two age groups*

Age group	*n*	Mean	SD
4–6.49 years	128	0.112	0.987
6.5+ years	58	–0.246	0.993

two populations overlapped and so this was not significant. An association between dichotomised age and pass rate at 3 months by treatment allocated was tested using the chi-squared test and showed no significant difference for either treatment (placebo group $p = 0.146$ and active group $p = 0.07$).

RESP score (OM8-30) and age group

There were no significant differences in this score at baseline in the active treatment group, but the younger group had a significantly worse score in the placebo group (U-test $p = 0.048$). Dichotomised age had no effect on the RESP score at 3 months – placebo group $p = 0.14$, active group $p = 0.57$ – to suggest an effect of the treatment on the adenoids in relation to age effects.

Adherence and age group

The analysis combined placebo and active groups as parents and children were blinded to treatment group. There was no difference in adherence at 1 month between the two age groups (Fischer's exact test, $p = 0.61$). At 3 months $p = 0.04$, which, although significant, probably did not represent a true difference as no linear-by-linear trend associations were found ($p = 0.40$).

Natural history and risk factors

Tympanometric criteria for resolution are the main efficacy outcomes for the entire follow-up period and, with a null trial for efficacy found, any contingent clinical effectiveness outcomes therefore require robust explanation. Very few trials actually report 9-month outcomes which are important in assessing clinical effectiveness, because with 41.9% non-resolution at 3 months post baseline treated and 34.7% non-resolution untreated and significant relapse rates for OME in both groups after 3 months of the intervention, the condition is likely to continue to cause and further NHS treatment in relation to re-attendance and referral. Unless there are over-riding concerns, the high proportions showing a natural resolution (similar treated or untreated) should be sufficient to support more widespread AM of children in a primary care setting for a 3-month period, over which time natural cure is probable with low-cost structured support potentially avoiding treatment and referral costs. The probability of cure is presented in *Figure 14* and assumes a null treatment effect and is based on all available data. These data are, however, based on individual children's time lines through the trial; so, for example, a child has a probability of only 0.21 of not being cured at any stage from 0 to 9 months, with a slightly higher probability of 0.28 of being cured at 1 month and remaining cured throughout the 9-month period. These data could be shared with patients in primary care during AM to show the likelihood of cure in more detail.

The study found only two significant potential risk factors at the $p < 0.02$ level (appropriate for number of variables ~50; see *Table 23*). The first was the same variable noted in the pre-specified

TABLE 22 *Risk estimates of tympanometric cure outcomes at 1, 3 and 9 months in terms of the two age groups*

Age group	1 month	3 months	9 months
4–6.49 years	0.66	0.76	0.57
	0.33–1.33	0.36–1.60	0.25–1.29
6.5+ years	1.36	3.56	0.85
	0.50–3.68	1.19–10.59	0.26–2.81

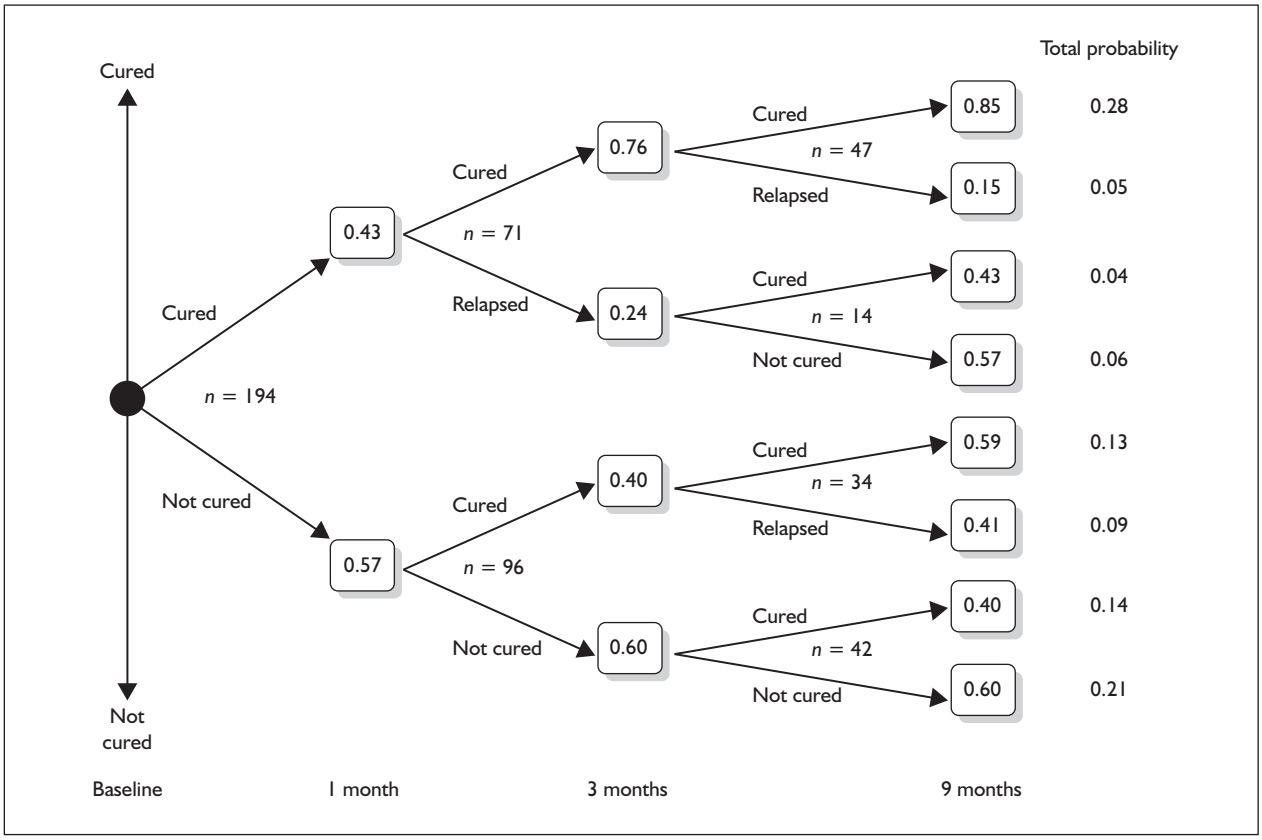

FIGURE 14 *Probabilities of cure, failure and relapse based on a null effect.*

logistic regression analysis, i.e. clinical severity score. The second was practice recruit type (high versus low recruiters) for cure or not at 3 months, but because there is no clear reason why this should be the case it may be a chance result. Age as a dichotomous variable is a subgroup of further interest found in Chapter 5 (*Figure 20a*) and so adjustments in probabilities could be made in relation to baseline severity and age for *Figure 14*, to help structured advice in primary care management.

Feasibility/exit interviews

Useful data were obtained from the exit interviews showing overall very high satisfaction levels whether receiving active or placebo treatment. This may have been in part a reflection of the detailed and structured nature of the observations and measurements given in addition to their standard care.

The semi-structured interview (Appendix 9) asked the parent (guardian) and child (1) for their comments on taking part in the study (good things, bad things, etc.), (2) whether they had any treatment preferences throughout the study and (3) what they will do with regard to the child's condition. The parent (guardian) and child were allowed to answer freely and the RN wrote down their responses as close to verbatim as possible.

(1) Comments on taking part in the study

Overall, parents (guardians) and children expressed that being in the study had been a very positive experience: 86.6% of responses (136/157) responded with positive comments, e.g. 'good', 'enjoyed', 'easy', 'happy', 'worthwhile', 'brilliant'. Of responses, 5.1% (8/157) were negative or bad, e.g. 'difficult', 'worse', 'did not like'. The remaining 8.3% (13/157) were indifferent, giving overall responses such as 'no comment' and 'nothing comes to mind'. Most of the parents (guardians) and children gave quite detailed responses to this question so these were broken down further by uncovering themes and counting how many times these themes were mentioned; examples of the responses are given below.

TABLE 23 *Potential risk factors: associations with poor outcome*

	1 month cured/not cured	3 months cured/not cured	Referred or not by 9 months
Age	NS	NS	NS
Gender	NS	NS	NS
Season randomised	NS	NS	NS
Day care	NS	NS	NS
Smoking in household	NS	NS	NS
Atopy	NS	$p < 0.05$	NS
Ethnicity	NS	NS	NS
Clinical severity score	$p < 0.02$	NS	$p < 0.05$
RESP score	$p < 0.05$	NS	$p < 0.05$
DEV score	NS	NS	NS
Age at first ear infection	NS	NS	NS
Frequency of GP surgery episodes in last 12 months for ear-related problems	NS	NS	NS
Parent reported frequency of ear infections in last 12 months for hearing-related problems	NS	NS	NS
Grommets inserted > 12 months prior to randomisation	NS	NS	NS
Adenoidectomy performed prior to randomisation	NS	NS	NS
Practice recruit type (high vs low recruiters)	NS	$p < 0.02$	NS

NS, not significant at $p \leq 0.05$.
Age, clinical severity score, and RESP and DEV scores were investigated using the Mann–Whitney test, the other data were dichotomous and therefore tested using the chi-squared or Fischer's exact tests.

Positive

Benefits for the parent and/or child

Educational/awareness raising:

- brought attention/awareness that there was a problem (25)
  I didn't realise that my daughter had glue ear until being asked to take part in the study
- problem was more serious than suspected (2)
  discovered he had worse ears than thought
- confirmed mother's suspicions (2)
  has confirmed what I [mother] thought about his hearing

Benefits of the intervention/procedures

- Spray worked/improvement seen (14)
  cured her snoring and night breathing a lot, it now allows everybody to sleep at night
- Spray didn't work but catalyst for getting problem sorted (2)
  as a result of the GNOME study, child has been referred to ENT
- Easy to follow procedures/spray easy to use (17)
  easy to do and child friendly and *not as much hassle as thought at first*

Benefits of participating in the study

- Reassuring as a parent to have expert input (9)
  reassuring to be taking part as child had more attention and ear tests than would normally
- Benefited child (no mention of spray) (6)
  really useful, benefited X
- Monitoring of child reassuring (15)
  good to know child's being monitored

- Child thought it was fun/parent and/or child enjoyed taking part/liked taking the spray (19)
  enjoyed coming to the surgery, likes the colouring in of the gnomes (RNs were supplied with sheets of gnome pictures and crayons for children to colour in)

- Good to involve children in the study/boosted confidence when attending appointments/felt important (5)
  [child] liked carrying card – felt important (all the study children were issued with a laminated card to carry at all times telling anyone that they were in the GNOME study and had emergency contact details); *child very good at taking spray, even reminding parents at night when they had forgotten*

Benefits for the wider community

- Happy to take part if it helps others (13)
  if it helps with future research I think it's a good thing to be in; hope it will help other children

- Pleased researchers interested in the problem (4)
  pleased that people are interested and trying to find another method of treatment

Negatives
For the parent

Practical problems with participating in the study:

- scheduling appointments sometimes difficult (3)
  sometimes difficult to keep all the appointments because of busy life or last-minute illness

- paperwork onerous (3)
  the only bad thing was all the paperwork and some of it was repetitive

For the parent and/or child
Problems with intervention:

- spray did not work/no benefit/had placebo (5)
  X's hearing didn't improve through trial

- spray was a nuisance/difficult to use/difficulty in remembering to use it/child did not like it (15)
  Bad [thing], trying to remember spray every day

- consequences of the spray – nosebleed, tickly, hurt, stung (6)
  no problem apart from nosebleeds when taking spray

Problems with measures:

- child did not like the audiometry (1)

Neutral
- Frustrating not knowing if spray got child better or was it just time or some other reason (2)

Post study
- Would like to know which treatment their child had (7)
- interested in results (3)

(2) Treatment preferences

Parents (guardians) responded to the question 'Did you have any treatment preference throughout the trial?' in nine different ways:

1. no preference ($n = 49$, 34%)
2. trial spray ($n = 43$, 30%)
3. only used spray so cannot state a preference ($n = 26$, 18%)
4. antibiotics ($n = 10$, 7%)
5. nasal drops ($n = 3$, 2%)
6. other sprays (e.g. beconase) ($n = 2$, 1%)
7. decongestant syrup ($n = 1$, 1%)
8. ear spray ($n = 1$, 1%)
9. no response ($n = 8$, 6%)

(3) Action to be taken by parent (guardian) after the end of the study

Parents (guardians) responded to the question 'What will you do now with regard to your child's condition?' in ten different ways:

1. wait/monitor ($n = 54$, 38%)
2. get referred or already referred ($n = 37$, 26%)
3. see GP ($n = 24$, 17%)
4. nothing/not concerned/happy at the moment ($n = 13$, 9%)
5. see GP to get study spray if successful ($n = 7$, 5%)
6. want spray not antibiotics ($n = 4$, 3%)
7. child's other problems more pressing (asthma) ($n = 2$, 1%)
8. self medicate/change behaviour, environment ($n = 1$, 1%)
9. try alternative (complementary) medicine ($n = 1$, 1%)

Summary

Ninety-seven per cent (157/162) of parents (guardians) returning for their child's last assessment at 9 months post baseline completed the exit interview with the RN. Overall, participation in the study had been a positive experience. There was some ambivalence about using the spray – some parents (guardians) found it hard to use, whereas others thought it was easy to use. However, many said that they would prefer to use the study spray over any other form of treatment. Future action regarding their child's condition was varied, but it was encouraging to see that most would not rush into anything, preferring to wait and see (AM).

Chapter 5

Health economic evaluation results

Analysis of resource use and costs

Table 24 provides a summary of the resource use values for each arm in the trial; results are presented separately for the active and placebo groups. There were no statistically significant differences between the trial arms in any category of resource use.

Medication was the least costly resource category in both trial arms (£6.04 and £11.09 for active and placebo groups respectively), while total hospital cost (inpatient and outpatient costs) was the most costly category (£335.47 and £342.05 for the active and placebo groups, respectively; *Table 25*). Statistical analysis revealed that, at 5% level, there were no significant differences between the two trial arms in the mean cost of inpatient admissions ($p = 0.94$), outpatient referrals ($p = 0.94$), medications ($p = 0.09$) or community services ($p = 0.88$). Mean total health service costs including mometasone, during the 9-month follow-up period were £450.04 in the active group and £448.57 in the placebo group, generating a mean cost difference of £1.52 that was not statistically significant ($p = 0.99$).

When multiple imputation was used to impute all missing data in costs, the average total health-care cost rose to £453.54 per child in the active treatment group and to £442.31 per child in the placebo group, reducing the difference between groups to £11.23 ($p = 0.91$).

Analysis of utility measures

Around 66–93% of children recruited to the trial after the protocol change (version 3, dated 5 May 2005) completed each utility measure at each time point. Furthermore, 19% (14/72) of children who entered the trial under the original protocol and had a period of AM completed one or more utility questionnaires at their 9-month follow-up.

TABLE 24 *Resource use values by resource item and allocation group*

	Active		Placebo		
Resource use variable	**Mean**	**SD**	**Mean**	**SD**	***p*-value[a]**
Number of GP contacts	1.67	1.75	1.98	2.03	0.25
Number of GP home visits	0.01	0.10	0.01	0.10	0.96
Number of GP telephone consultations	0.08	0.31	0.10	0.53	0.70
Number of GP out of hours consultations	0.16	0.47	0.08	0.30	0.12
Number of practice nurse contacts	0.38	0.81	0.44	0.86	0.61
Number of practice nurse telephone consultations	0.03	0.17	0.07	0.29	0.28
Number of district nurse home visits	0.00	0.00	0.00	0.00	N/A
Number of health visitor contacts	0.04	0.28	0.07	0.37	0.58
Number of health visitor home visits	0.02	0.14	0.03	0.22	0.75
Number of speech therapist contacts	0.03	0.17	0.03	0.17	1.00
Number of contacts with other community health-care professionals	0.07	0.36	0.03	0.17	0.29
Number of hospital outpatient referrals	0.53	0.77	0.47	0.66	0.56
Number of hospital admissions	0.18	0.54	0.24	0.47	0.23
Number of investigative tests	0.03	0.17	0.09	0.32	0.07

a *p*-value calculated using two-tailed Student's *t*-tests assuming unequal variance.

TABLE 25 *Mean costs by cost category and allocation group (pound sterling, 2006–7 prices)*

	Active			Placebo			
Cost category	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	***p*-value**
Complete case analysis: including only those patients with complete cost data							
Hospital outpatient costs	*54.49*	*83.38*	*100*	*53.66*	*80.41*	*107*	*0.94*[a]
Hospital inpatient costs	*280.98*	*767.06*	*100*	*288.39*	*611.11*	*107*	*0.94*[a]
Total hospital costs	335.47	784.67	100	342.05	639.95	107	0.95[a]
Medication costs excluding mometasone	6.04	13.23	100	11.09	27.32	107	0.09[a]
Community service costs	92.92	136.90	100	95.44	99.26	107	0.88[a]
Total health-care costs excluding mometasone	434.43	842.79	100	448.57	647.29	107	0.89[a]
Topical mometasone	15.66	0.00	100	NA	NA	NA	NA
Total health-care costs including mometasone	450.09	842.79	100	448.57	647.29	107	0.99[a]
Including missing values imputed using multiple imputation							
Total health-care costs	453.54	847.35	105	442.31	643.23	112	0.91[b]

a *p*-value calculated in Microsoft EXCEL using two-tailed Students' *t*-tests assuming unequal variance.
b Based on a two-tailed *t*-test in which SEs were calculated using Equation (1).

Overall, 45.4% (886/1953) of all potential utility measurements were missing, of which up to 69% (607/886) resulted from the late introduction of utility measures into the study.

The mean utilities in the placebo group were higher than those in the active treatment group for all measures and at almost all time points (*Table 26*). However, none of the differences between treatment arms reached statistical significance. A slight imbalance in utilities was also present at baseline.

The mapping analysis, which used regression analyses to 'map' responses from the OM8-30 questionnaire onto the utility measures (Appendix 15) had the potential to fill around 48% of the gaps in the utility data, such that 23.7% (463/1953) of child observations had missing utility values. By contrast, multiple imputation could fill all missing data in both costs and utilities.

The inclusion of mapped utility values or values estimated using multiple imputation had relatively little impact on mean utilities and there continued to be no significant difference between treatment groups (*Table 27*). As was observed in the complete case analysis (see *Table 26*), utilities were not significantly higher in the placebo group than in the active treatment group when mapped or imputed values were included.

The utilities calculated at individual time points were used to calculate the QALYs gained from treatment using the methods described in Chapter 2, Calculations of utilities and quality-adjusted life-years. Calculation of total QALYs with no adjustment for baseline utilities suggested that there was no statistically significant difference between the active and placebo arms of the trial in terms of the QALYs accrued over the 9-month follow-up period (*Table 28*). However, there was a trend towards fewer QALYs being accrued in the active arm of the trial than in the placebo arm regardless of the instrument used or the inclusion of mapped utilities.

As the placebo group had better health-related QoL at baseline (see *Tables 26* and *27*), not allowing for the difference in baseline utilities means that the unadjusted QALYs shown in *Table 28* underestimate the QALY benefits (or overestimate the QALY loss) from treatment.

TABLE 26 *Results of the utility measures used in the trial: complete cases only*

		Utility									
		Intranasal steroids				Placebo				*p*-value	
Measure	Time	Mean	SE	*N*	% full health (*n*/*N*)	Mean	SE	*N*	% full health (*n*/*N*)	Mean utility	% full health
HUI3	BL	0.7767	0.0266	63	20.63 (13/63)	0.7787	0.0290	69	27.54 (19/69)	0.9592[a]	0.3295[b]
	3	0.8041	0.0306	56	32.14 (18/56)	0.8770	0.0232	54	46.3 (25/54)	0.0614[a]	0.2157[b]
	9	0.8804	0.0278	56	48.21 (27/56)	0.8806	0.0258	54	48.15 (26/54)	0.9958[a]	0.6621[b]
EQ-5D$_5$	BL	0.8869	0.0294	67	61.19 (41/67)	0.9313	0.0121	68	63.24 (43/68)	0.1625[a]	0.5827[b]
HUI2	BL	0.8411	0.0216	61	18.03 (11/61)	0.8520	0.0172	70	18.57 (13/70)	0.6912[a]	0.6219[b]
	3	0.8809	0.0218	56	35.71 (20/56)	0.9113	0.0157	53	43.4 (23/53)	0.2652[a]	0.3588[b]
	9	0.9165	0.0177	57	47.37 (27/57)	0.9054	0.0185	54	42.59 (23/54)	0.6649[a]	0.4621[b]
	3	0.9522	0.0111	56	73.21 (41/56)	0.9169	0.0294	58	70.69 (41/58)	0.2694[a]	0.5449[b]
	9	0.9212	0.0273	58	75.86 (44/58)	0.9451	0.0140	57	73.68 (42/57)	0.4396[a]	0.5579[b]

BL, baseline.
a Based on a two-tailed *t*-test assuming equal variances.
b Based on a chi-squared test.

For the purposes of assessing the clinical benefits/harms from treatment, two different forms of baseline adjustment were conducted. The first method involved simply subtracting the child's baseline utility from his or her on-treatment utilities before calculating QALYs as before. The second method used linear regression to calculate the effect of treatment allocation on the QALYs accrued, adjusting for baseline utility. For simplicity, and to facilitate consistency between the CEA and CUA, only the first method was used in the CUA. Neither method found there to be a significant difference in QALYs between trial groups for any utility instrument (*Table 29*).

In conclusion, the analysis of utility measures confirms the results of the clinical outcome measures, finding no statistically significant difference in QALYs or utilities between the trial groups.

Results of the cost-effectiveness analysis

Base case

The CEA evaluated the cost-effectiveness of intranasal steroids in terms of natural units, calculating the cost per additional child cured of OME. In the base-case analysis, a composite end point of outcomes at 1 and 3 months was used, whereby children were considered to be cured if they were found to be free of OME (based on tympanometry) at either 1 or 3 months. This differs from the primary outcome used in the clinical analysis (cure at 1 month, adjusted for covariates), although the definition used was varied in sensitivity analyses. The incremental cost-effectiveness of intranasal steroids is shown in *Table 30*.

As described in Chapter 2, Methods for dealing with missing data, the base-case analysis used the

TABLE 27 *Results of the utility measures used in the trial: including utility values that have been mapped from OM8-30 responses and values imputed through multiple imputation*

		Utility						
		Intranasal steroids			Placebo			
Measure	Time	Mean	SE	*n*	Mean	SE	*n*	*p*-value
Including mapped utility values								
HUI3 – facet-level model	BL	0.7644	0.0192	94	0.7725	0.0220	97	0.7809[a]
	3	0.8103	0.0229	83	0.8520	0.0184	78	0.1614[a]
	9	0.8550	0.0230	74	0.8745	0.0216	68	0.5388[a]
HUI3 – domain-level model	BL	0.7678	0.0191	94	0.7756	0.0215	97	0.7878[a]
	3	0.8048	0.0226	83	0.8455	0.0184	78	0.1675[a]
	9	0.8527	0.0227	75	0.8716	0.0215	68	0.5466[a]
HUI2	BL	0.8374	0.0148	94	0.8498	0.0130	97	0.5286[a]
	3	0.8761	0.0161	83	0.8911	0.0124	77	0.4689[a]
	9	0.8979	0.0149	75	0.9021	0.0153	68	0.8422[a]
EQ-5D$_5$	BL	0.8949	0.0204	97	0.9272	0.0087	97	0.1466[a]
	3	0.9332	0.0140	82	0.9207	0.0216	79	0.6246[a]
	9	0.9251	0.0206	77	0.9435	0.0115	70	0.4492[a]
Including values imputed using multiple imputation								
HUI3	BL	0.7578	0.0436	105	0.7657	0.0364	112	0.8154[b]
	3	0.7757	0.0614	105	0.8359	0.0577	112	0.0731[b]
	9	0.8755	0.0271	105	0.8712	0.0379	112	0.9079[b]
HUI2	BL	0.8489	0.0265	105	0.8547	0.0221	112	0.8309[b]
	3	0.8901	0.0310	105	0.9006	0.0216	112	0.6267[b]
	9	0.9189	0.0166	105	0.8966	0.0242	112	0.3230[b]
EQ-5D$_5$	BL	0.8844	0.0391	105	0.9134	0.0218	112	0.4241[b]
	3	0.9371	0.0193	105	0.9166	0.0200	112	0.4020[b]
	9	0.9275	0.0241	105	0.9234	0.0231	112	0.9043[b]

a Based on a two-tailed *t*-test assuming equal variances; SE = SD/$\sqrt{n}$.
b Based on a two-tailed *t*-test in which SEs were calculated using Equation (1).

techniques of multiple imputation[94] to impute cost and clinical outcome data for any children who were missing such information. In total, 17 children were missing clinical outcome data, while 10 were missing cost data. Due to the relatively small degree of missing data for these outcomes, taking account of the variability between multiple imputation datasets had relatively little effect on estimates of the variance for either costs or the clinical outcome measure. Overall, 3.49% of the variance around the incremental efficacy and 2.58% of the variance around the incremental cost was due to uncertainty about the true value of missing data.

Within the base-case analysis, which included all 217 children randomised, the average cost was £454 per child in the active treatment group, compared with £442 per child in the placebo group (see *Table 32*). The costs presented in *Tables 30–32* differ from those presented in the penultimate entry in *Table 25* as the latter represents a complete case analysis including only the 207 patients with complete cost data, whereas the base-case analyses presented in *Tables 30–32* include all 217 patients randomised, including imputed cost values for the 10 patients with missing cost data. However, there was no statistically significant difference in costs between the two groups, with 53.72% of bootstrap

TABLE 28 *Total QALYs accrued with no adjustment for baseline values*

	Total (unadjusted) QALYs per child						
	Intranasal steroids			Placebo			
Measure	**Mean**	**SE**	***n***	**Mean**	**SE**	***n***	***p*-value**
Complete cases only[a]							
HUI3	0.6099	0.0197	40	0.6483	0.0162	43	0.1340[c]
HUI2	0.6691	0.0135	40	0.6741	0.0118	42	0.7798[c]
EQ-5D$_5$	0.6962	0.0125	44	0.6928	0.0151	46	0.8642[c]
Including mapped utilities[b]							
HUI3 facet model	0.6131	0.0140	82	0.6402	0.0119	76	0.1454[c]
HUI3 domain model	0.6107	0.0139	82	0.6376	0.0117	76	0.1446[c]
HUI2	0.6575	0.0100	82	0.6691	0.0083	76	0.3800[c]
EQ-5D$_5$	0.6924	0.0082	84	0.6978	0.0094	78	0.6600[c]
Including missing utilities estimated using multiple imputation							
HUI3	0.6045	0.0308	105	0.6270	0.0291	112	0.2181[d]
HUI2	0.6696	0.0146	105	0.6688	0.0089	112	0.9427[d]
EQ-5D$_5$	0.6939	0.0115	105	0.6888	0.0129	112	0.7350[d]

a Includes only those children who fully completed the relevant utility measure at all three time points.
b Includes all children with baseline utility values and data at either 3 or 9 months based on either direct completion of generic utility measures or values calculated from the OM8-30 mapping algorithm.
c Based on a two-tailed *t*-test assuming equal variances; SE = SD/$\sqrt{n}$.
d Based on a two-tailed *t*-test in which SEs were calculated using Equation (1).

replicates finding steroids to be more costly than placebo.

Intranasal steroids were therefore dominant over placebo, being more effective and less costly. However, there was substantial uncertainty around this finding. The variability around the base-case estimates of cost-effectiveness, which is shown in the cost-effectiveness plane displayed in *Figure 15*, indicates that there is a 19.42% chance that steroids are dominated by placebo, in addition to a 34.89% chance that steroids dominate placebo. The dots in *Figure 15* occur in discrete stripes as within each bootstrap replicate conducted in the trial an integer number of children will have been cured in each treatment arm.

The CEAC shown in *Figure 16* indicates that the higher the value that decision-makers place on an additional case of OME cured, the higher the probability that intranasal steroids will be more cost-effective. At the notional willingness to pay threshold (or ceiling ratio) of £1000 per additional case of OME cured, the probability that use of intranasal steroids is cost-effective was estimated to be 56.4%. Although no previous research has empirically shown how much society or the NHS may or should be willing to pay to cure a case of OME, this figure may be in the region of £1000 based on surgery costing around £1000 per child treated.[4,100,101] At the notional willingness to pay threshold of £3000 per additional case of OME cured, the probability that intranasal steroids are cost-effective increased to 63.2%.

Sensitivity analyses

Sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the ICER (*Figures 17* and *18* and *Table 30*).

In total, 17 children (8.5% of the trial population) were missing data for the composite clinical outcome (cure of OME at 1 or 3 months), while 10 were missing cost data. Subsequently, sensitivity analyses employed a number of different imputation techniques to test the impact of

TABLE 29 *Incremental QALY gain from treatment following adjustment for differences in baseline utilities*

	Incremental QALY gain from treatment (active treatment minus placebo)			
Utility measure	**Mean**	**SE**	***n***	***p*-value**
Indexing to baseline (baseline utility subtracted from on-treatment utility values): complete cases only[a]				
HUI3	0.00909	0.02471	83	0.714[b]
HUI2	0.03623	0.01840	82	0.052[b]
EQ-5D$_5$	0.02695	0.03069	90	0.382[b]
Indexing to baseline (baseline utility subtracted from on-treatment utility values): including mapped values[c]				
HUI3 facet model	–0.06147	0.04433	146	0.168[b]
HUI3 domain model	–0.00030	0.01627	158	0.985[b]
HUI2	0.00880	0.01191	158	0.461[b]
EQ-5D$_5$	0.02377	0.01915	162	0.216[b]
Indexing to baseline (baseline utility subtracted from on-treatment utility values): missing data estimated using multiple imputation				
HUI3	–0.0166	0.0235	217	0.480[d]
HUI2	0.0052	0.0155	217	0.737[d]
EQ-5D$_5$	0.0268	0.0218	217	0.220[d]
Regression adjustment for baseline utility: complete cases only[a]				
HUI3	–0.01399	0.01869	83	0.456[e]
HUI2	0.01504	0.01271	82	0.240[e]
EQ-5D$_5$	0.00874	0.01841	90	0.636[e]
Regression adjustment for baseline utility: including mapped values[c]				
HUI3 facet model	–0.01162	0.01349	158	0.390[e]
HUI3	–0.01157	0.01354	158	0.394[e]
HUI2	–0.00017	0.00972	158	0.986[e]
EQ-5D$_5$	0.00096	0.01174	162	0.935[e]
Regression adjustment for baseline utility: missing data estimated using multiple imputation				
HUI3	–0.01986	0.01627	217	0.224[e]
HUI2	0.00277	0.00935	217	0.767[e]
EQ-5D$_5$	0.53601	0.03982	217	0.431[e]

a Includes only those children who fully completed the relevant utility measure at all three time points.
b Based on a two-tailed *t*-test assuming equal variances; SE = SD/$\sqrt{n}$.
c Includes all children with baseline utility values and data at either 3 or 9 months (whether derived from direct completion of generic utility measures or from the OM8-30 mapping algorithm).
d Based on a two-tailed *t*-test in which SEs were calculated using Equation (1).
e Based on the statistical significance of the coefficient for treatment allocation within the regression assessing the impact of treatment and baseline utility on total QALYs. The 'micombine' option was used for the analysis that included data from multiple imputation.

different assumptions for filling in such gaps in the clinical outcome data.

Within the base-case analysis, the cost of tympanometry was excluded from total costs because it is not routinely used in UK general practice at present. A sensitivity analysis investigated the impact of including the cost of baseline tympanometric assessment (£18.81 per child; see Appendix 14) to the costs incurred in both arms of the model. Given that the total cost was increased by the same amount in both

arms of the model, this change had no impact on incremental cost-effectiveness (see *Table 30* and *Figure 17a,b*).

Making the most optimistic possible assumptions about missing clinical outcome data (assuming that all children who were missing data on clinical outcomes had been cured by 1 or 3 months) increased the proportion of children in the treatment group who were assumed to have responded by 0.0176 and in the placebo group by 0.0355 (see *Table 30* and *Figure 17a,c*). This analysis also affected the incremental cost, which fell to £1.52 per child, as this analysis excluded those children who had missing cost data. Although the point estimate of the ICER for active treatment relative to placebo fell to £105 per additional case cured due to the reduction in incremental costs, the probability that treatment was cost-effective at a £1000 per cure threshold increased to 36% as the probability that treatment was cost-effective fell to 59%.

Making the most pessimistic assumptions and running a form of ITT analysis, whereby all children with missing clinical outcome data were assumed not to have been cured had the reverse effect, increased the probability that active treatment is more effective than placebo to 76% and increased the probability that treatment is cost-effective if the NHS is willing to pay £1000 per case of OME cured to 64% (see *Table 30* and *Figure 17a,d*).

The impact of adjusting for missing cost data was also investigated using mean imputation: within this simple imputation technique, the total NHS costs for any child with missing cost data were simply assumed to be equal to the mean cost for that study arm, and clinical outcomes for those children with missing clinical outcome data were assumed to be equal to the probability of response in that study arm (see *Table 30* and *Figure 17a,e*). Similarly, the mean clinical outcome data for children with missing outcomes at both 1 and 3 months was based on the mean for that study arm. This analysis had minimal impact on the results (see *Figure 17a,f*) as only 10 children had missing cost data and 17 had missing outcome data.

In the complete case analysis, children with missing data on either costs or the composite clinical outcome were excluded from the analysis (see *Table 30* and *Figure 18a,b*). Based on this analysis, the active treatment group had higher costs than the placebo group; however, the difference was not statistically significant. In this analysis, the point estimate of the ICER showed active treatment as costing £178 per additional case of OME cured, with a 55% probability of being cost-effective at a ceiling ratio of £1000 per case cured.

Three sensitivity analyses evaluated the impact of evaluating clinical outcomes at 1, 3 and 9 months after start of treatment, instead of using a composite end point of cure at either 1 or 3 months (see *Figure 18*). Because outcomes at 1 and 3 months are closely correlated with the composite end point, these three analyses were based on a separate run of multiple imputation in which the composite clinical end point was replaced with outcomes at the three individual time points. This means that the imputed costs used in these analyses differ slightly from those used in the base-case analysis.

The analysis using outcomes at 1 month matches the time point of the primary outcome measure in the trial. The proportion of children whose OME was cured within 1 month of starting treatment was lower in the active treatment group than in the placebo group (see *Table 30* and *Figure 18a,c*). Subsequently, basing clinical outcomes on the proportion of cases cured by the 1-month follow-up rather than a composite end point including cures by either 1 or 3 months suggested that treatment with intranasal steroids would be dominated by placebo, being more costly and less effective than no treatment. If the NHS were willing to pay £1000 to gain one less cure of OME in order to accrue savings of at least £1000, active treatment would have a 37% probability of being cost-effective.

However, as in the base-case analysis, assessing outcome at 3 months suggested that treatment is slightly (but not significantly) more effective than placebo in terms of the cost per case of OME cured. When clinical outcomes were based on assessments at 3 months, active treatment cost £159 per case of OME cured and had a 71% chance being cost-effective at a £1000 ceiling ratio (see *Table 30* and *Figure 18a,d*).

The proportion of children whose OME was cured within 9 months of starting treatment was also lower in the active treatment group than in the placebo group (see *Table 30* and *Figure 18a,e*). The probability of treatment being cost-effective at a ceiling ratio of £1000 when outcomes were assessed at this time point was 29.56%, and treatment was dominated by placebo.

TABLE 30 *CEA results for the base-case analysis and sensitivity analyses (pound sterling, 2006–7 prices)*

	Total costs (95% CI)			Proportion of children cured (95% CI)				Probability that steroid arm is		Probability treatment cost-effective at ceiling ratio			Probability steroid arm is	
Analysis	**Active**	**Placebo**	**Difference**	**Active**	**Placebo**	**Difference**	**Cost/OME cured**	**Dominant**	**Dominated**	**£500**	**£1000**	**£2000**	**More effective**	**Less costly**
Base case (placebo $n = 112$; active treatment $n = 105$; 5000 bootstrap replicates for each of five data sets)	£454 (£283 to £624)	£442 (£315 to £570)	£11 (–£199 to £222)	0.6324 (0.5383 to 0.7265)	0.600 (0.503 to 0.697)	0.0324 (–0.1032 to 0.168)	£347	34.89%	19.42%	51.86%	56.40%	61.01%	65.43%	46.28%
Sensitivity analyses														
Complete case analysis (placebo $n = 98$; active treatment $n = 95$; 1000 bootstrap replicates for a single data set that excludes missing values)	£442 (£273 to £610)	£436 (£312 to £561)	£5 (–£204 to £215)	0.632 (0.534 to 0.729)	0.602 (0.505 to 0.699)	0.0295 (–0.1083 to 0.1674)	£178	32.90%	20.70%	52.40%	55.20%	60.70%	62.60%	49.60%
Best case analysis (placebo $n = 107$; active treatment $n = 100$; 1000 bootstrap replicates for a single data set that excludes missing values)	£450 (£285 to £615)	£449 (£326 to £571)	£2 (–£104 to £207)	0.6500 (0.556 to 0.744)	0.635 (0.544 to 0.727)	0.0145 (–0.1167 to 0.1457)	£105	33.90%	22.70%	40.82%	36.12%	33.82%	59.20%	52.00%
Worst case/ITT analysis (placebo $n = 107$; active treatment $n = 100$; 1000 bootstrap replicates for a single data set that excludes missing values)	£450 (£285 to £615)	£449 (£326 to £571)	£2 (–£204 to £207)	0.600 (0.503 to 0.697)	0.551 (0.457 to 0.646)	0.0486 (–0.0866 to 0.1838)	£31	39.80%	13.90%	57.60%	64.20%	69.70%	76.20%	49.70%
Cost/response at 1 month (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for each of five data sets)	£449 (£283 to £615)	£436 (£312 to £561)	£13 (–£192 to £218)	0.421 (0.3154 to 0.5265)	0.4571 (0.3559 to 0.5584)	–0.0362 (–0.1785 to 0.1061)	Dominated (–£360)	16.38%	38.76%	40.42%	36.98%	33.84%	29.14%	47.04%

Analysis	Total costs (95% CI)			Proportion of children cured (95% CI)			Cost/OME cured	Probability that steroid arm is		Probability treatment cost-effective at ceiling ratio			Probability steroid arm is	
	Active	Placebo	Difference	Active	Placebo	Difference		Dominant	Dominated	£500	£1000	£2000	More effective	Less costly
Cost/response at 3 months (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for each of five data sets)	£449 (£282 to £617)	£436 (£311 to £561)	£13 (–£196 to £222)	0.5981 (0.4883 to 0.7079)	0.5161 (0.411 to 0.6211)	0.082 (–0.0688 to 0.2328)	£159	41.40%	6.88%	59.98%	70.84%	79.70%	85.56%	46.44%
Cost/response at 9 months (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for each of five data sets)	£449 (£279 to £620)	£436 (£310 to £563)	£13 (–£201 to £227)	0.5333 (0.417 to 0.6496)	0.5964 (0.4753 to 0.7175)	–0.0631 (–0.2292 to 0.103)	Dominated (–£206)	10.94%	43.92%	36.48%	29.56%	24.60%	19.72%	46.70%
Mean imputation (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for a single data set that excludes missing values)	£450 (£293 to £607)	£449 (£331 to £566)	£2 (–£195 to £198)	0.635 (0.545 to 0.724)	0.608 (0.521 to 0.694)	0.027 (–0.0976 to 0.1516)	£56	37.90%	19.90%	57.30%	60.50%	63.10%	66.30%	51.70%
Parental cost estimates (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for each of five data sets)	£458 (£251 to £666)	£274 (£149 to £399)	£185 (–£72 to £441)	0.6324 (0.5378 to 0.7269)	0.600 (0.5035 to 0.6965)	0.0324 (–0.1038 to 0.1686)	£5704	3.09%	29.86%	62.60%	64.44%	65.48%	65.34%	4.06%
Tympanometry (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for each of five data sets)	£472 (£306 to £639)	£461 (£336 to £586)	£11 (–£192 to £214)	0.6324 (0.5385 to 0.7263)	0.600 (0.5028 to 0.6972)	0.0324 (–0.1042 to 0.1689)	£3467	34.89%	19.11%	52.88%	57.74%	62.32%	65.50%	46.50%

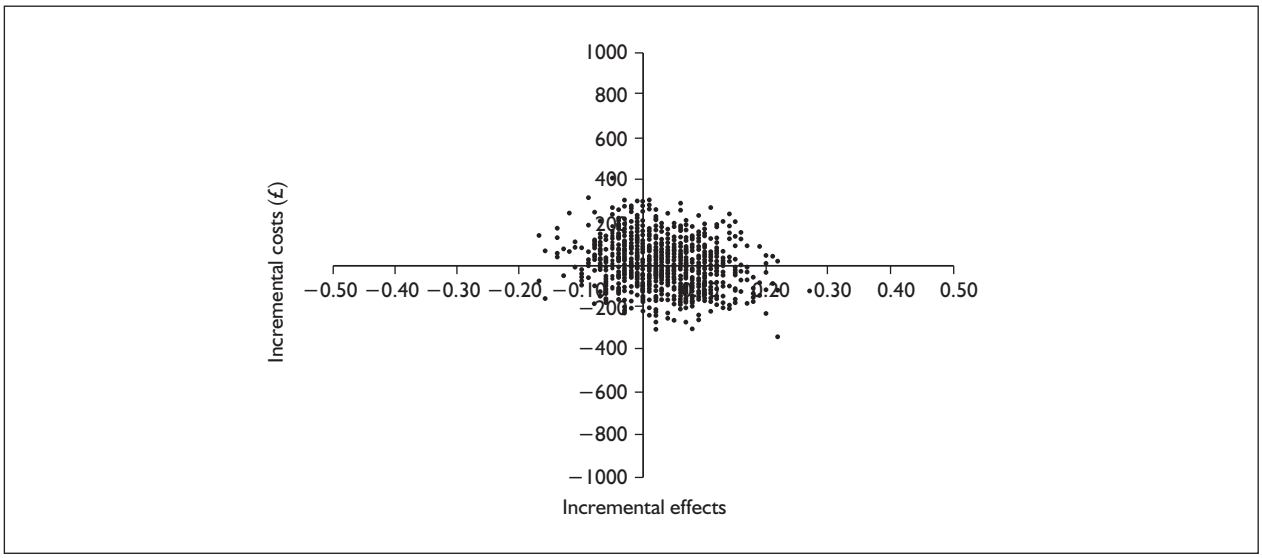

FIGURE 15 *Cost-effectiveness plane for base-case analysis. The scatter graph shows the mean difference in costs and in the proportion of children cured based on the bootstrapping analysis. For clarity, only the first 200 bootstrap replicates drawn from each of the five multiple imputation data sets are shown.*

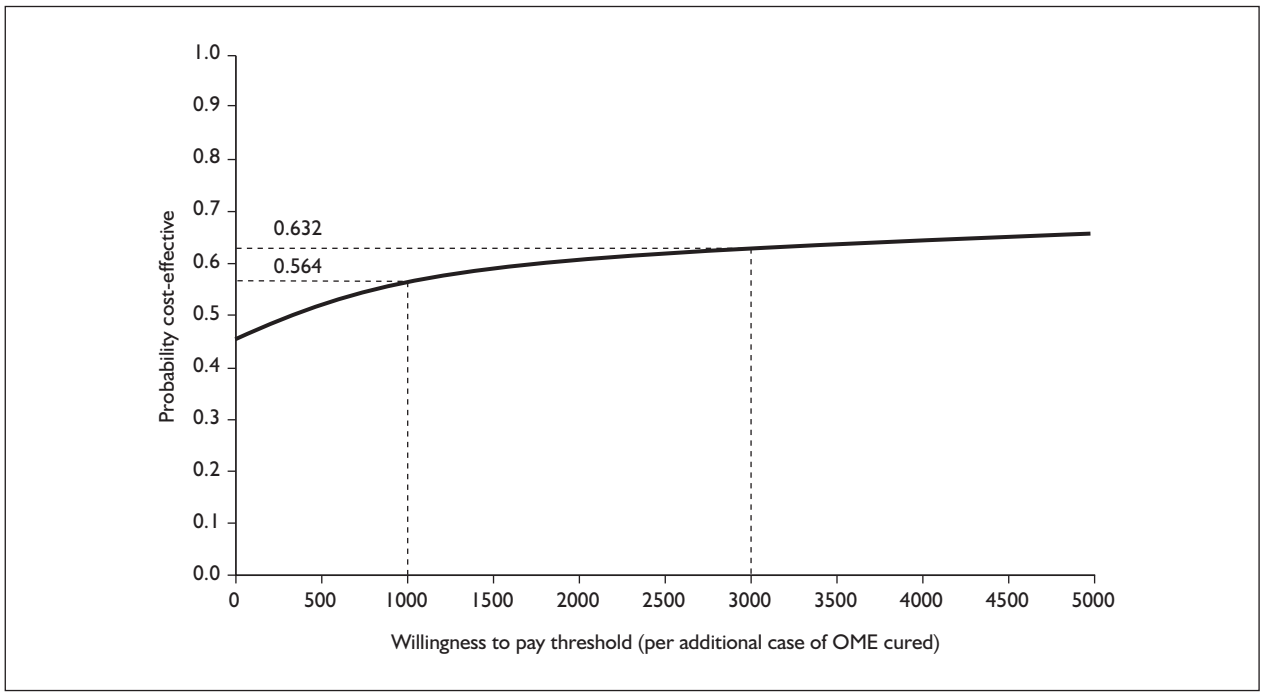

FIGURE 16 *CEAC for the base-case CEA. The dotted and dashed lines indicate the ceiling ratios or willingness to pay thresholds described in the text (£1000 and £3000 per case of OME cured respectively).*

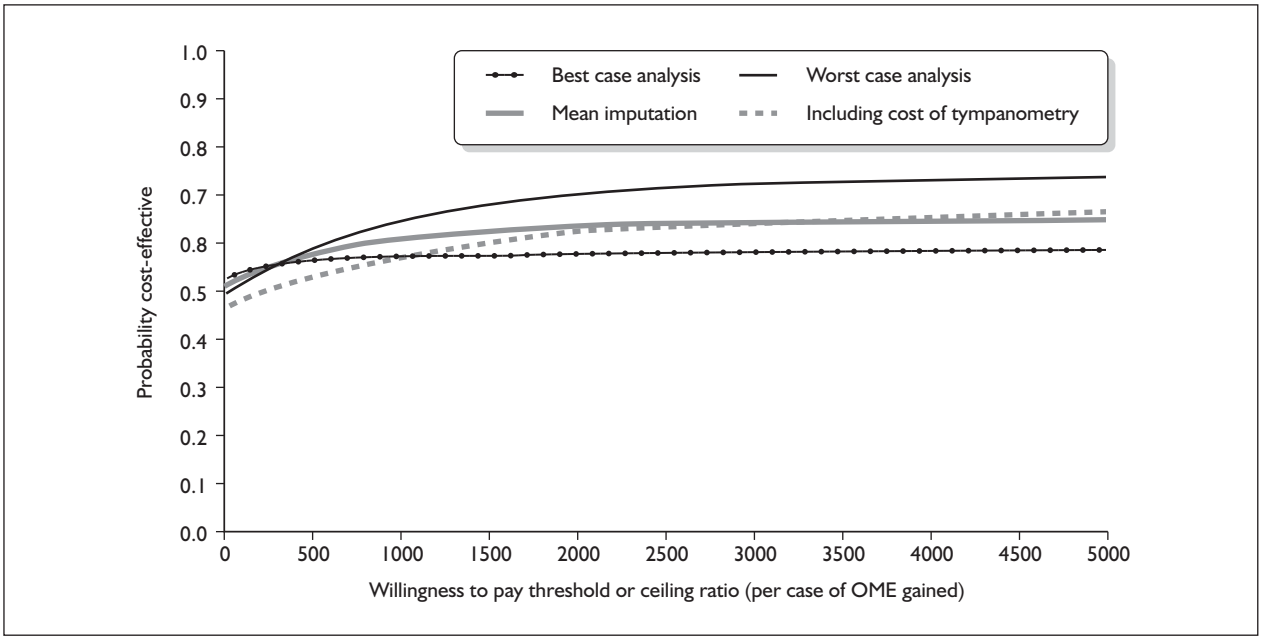

FIGURE 17a *CEACs for sensitivity analyses using different assumptions or methods. Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME.*

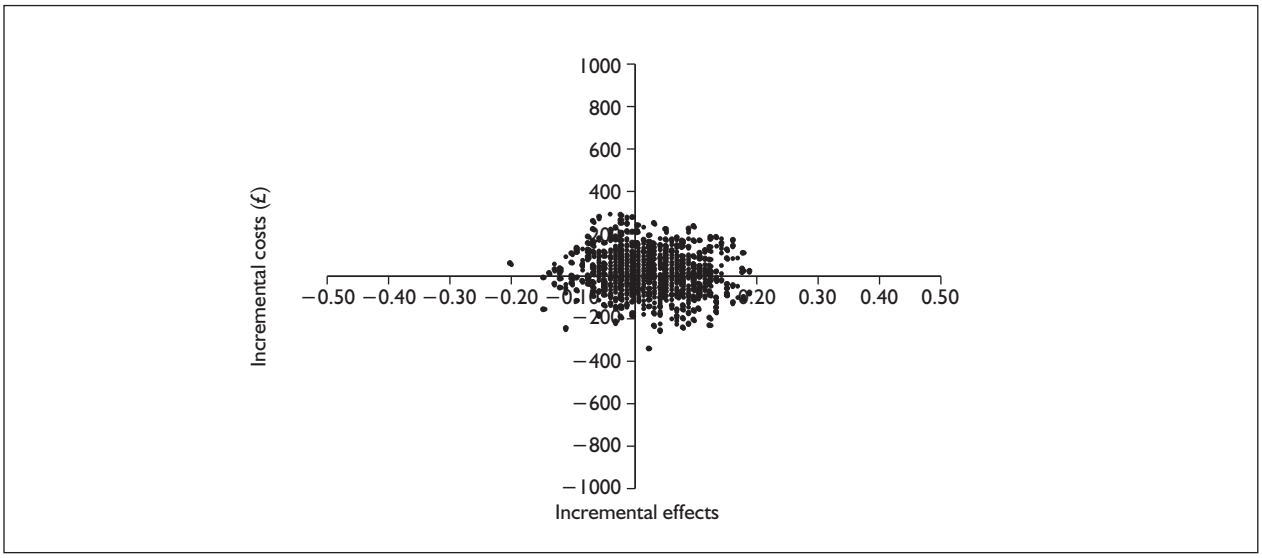

FIGURE 17b *Including incremental cost of tympanometry: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured based on 1000 bootstrap replicates. In this analysis, the cost of tympanometric assessment at baseline (Appendix 14) was added to the total costs for all children in both arms of the trial. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed datasets are shown; all values are per child.*

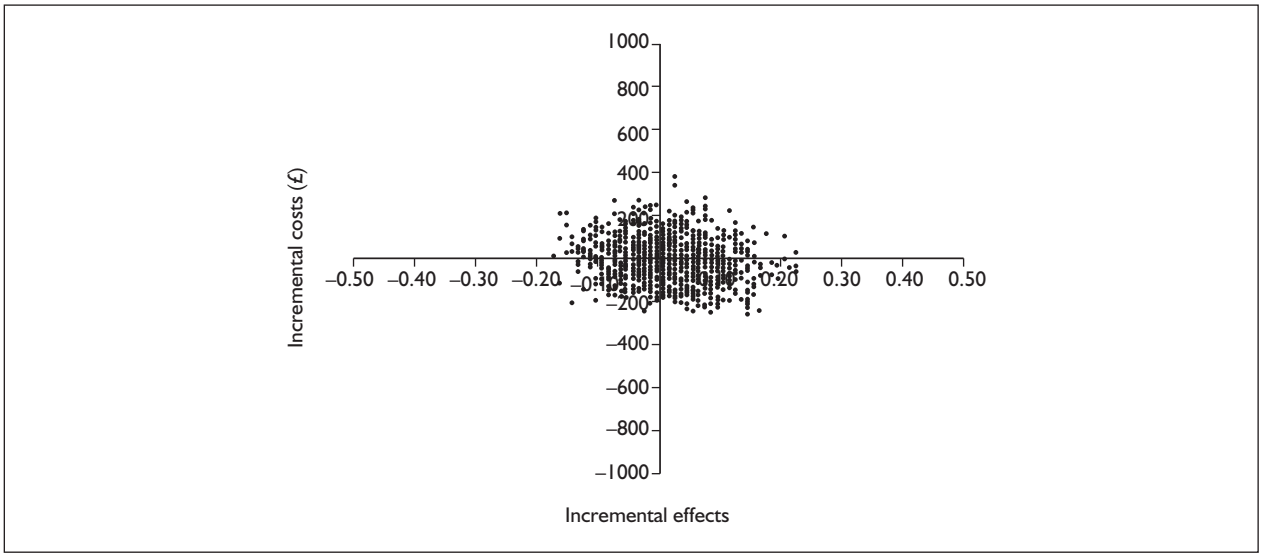

FIGURE 17c *Best case analysis: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured based on 1000 bootstrap replicates. In this analysis, all children with missing data for the primary outcome measure were assumed to be cured.*

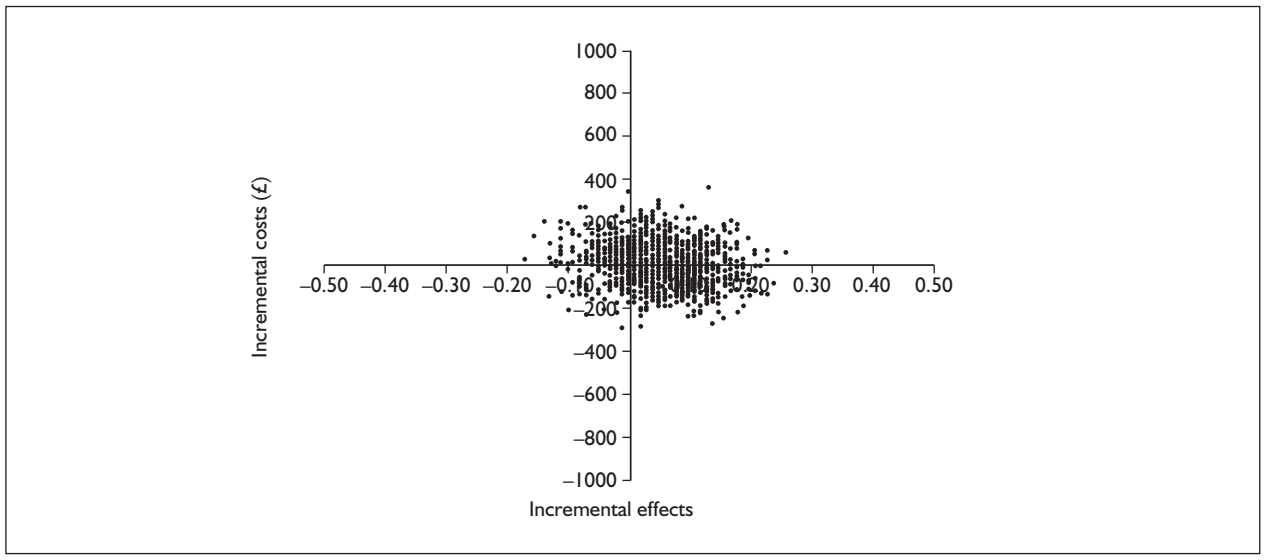

FIGURE 17d *Worst case/ITT analysis: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured based on 1000 bootstrap replicates. In this analysis, all children with missing data for the primary outcome measure were assumed to have not been cured.*

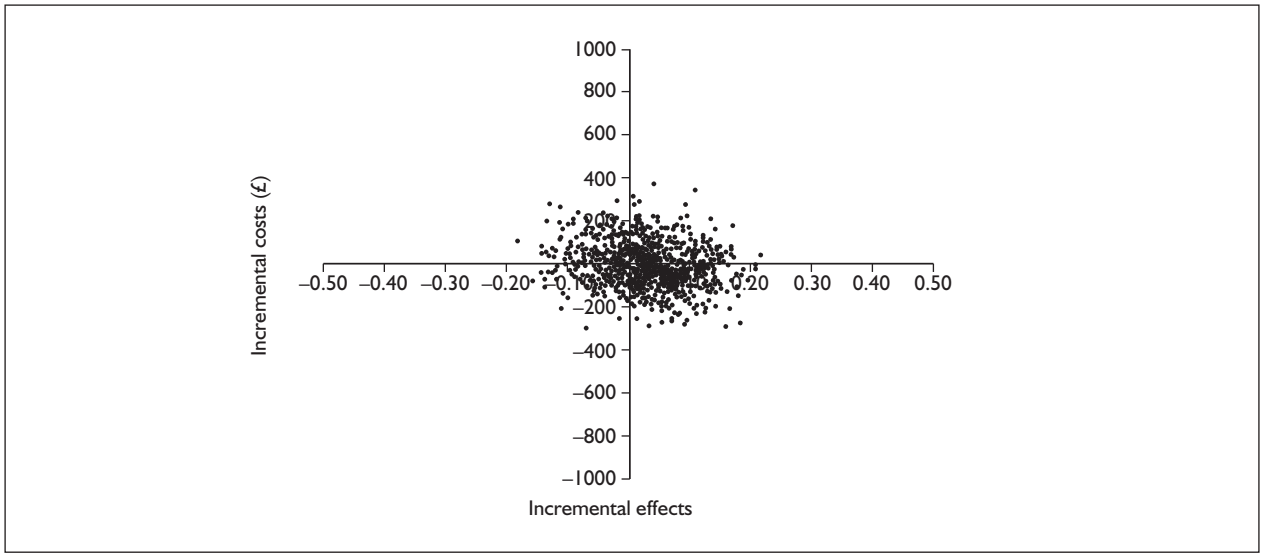

FIGURE 17e *Mean imputation of missing cost and clinical outcome data: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured based on 1000 bootstrap replicates. In this analysis, all children with missing cost data were assumed to have total treatment costs equal to the mean total cost across children in the relevant study arm and similarly with clinical outcomes.*

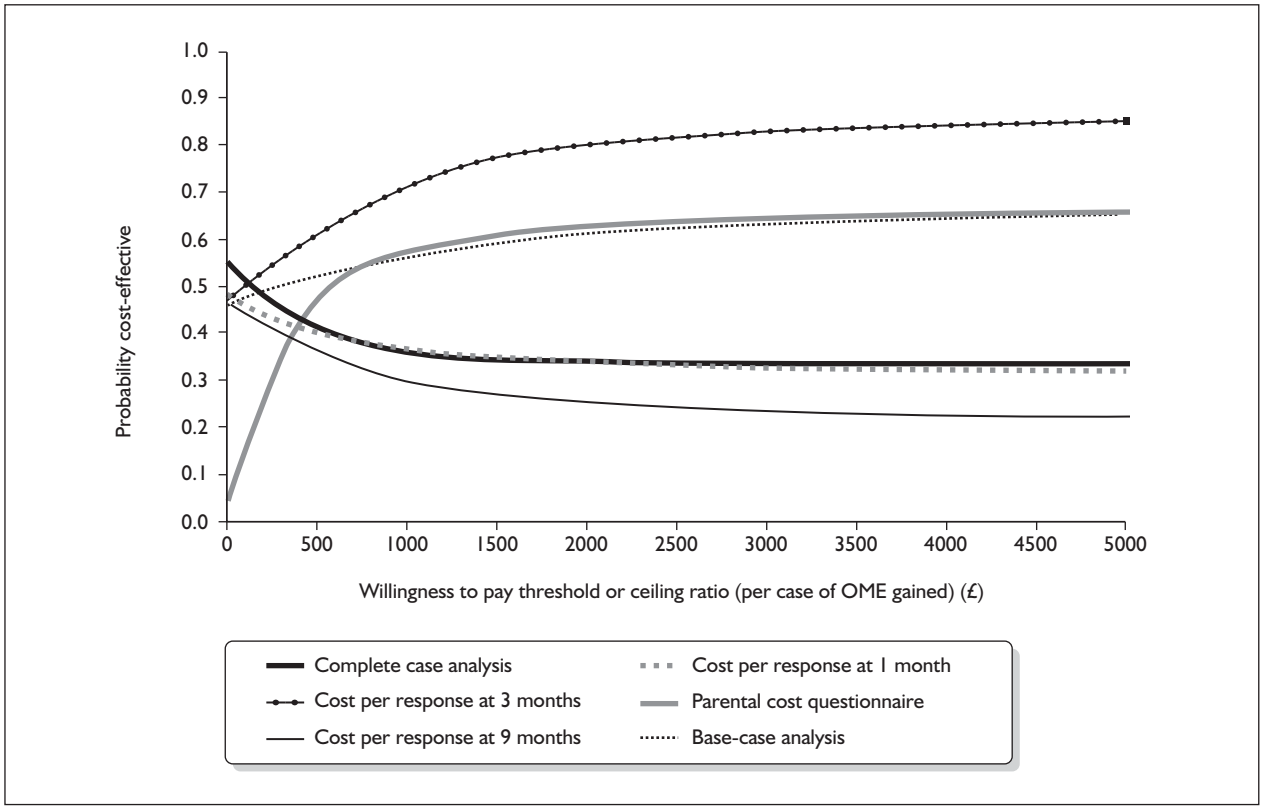

FIGURE 18a *CEACs for sensitivity analyses using different assumptions or methods. Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME.*

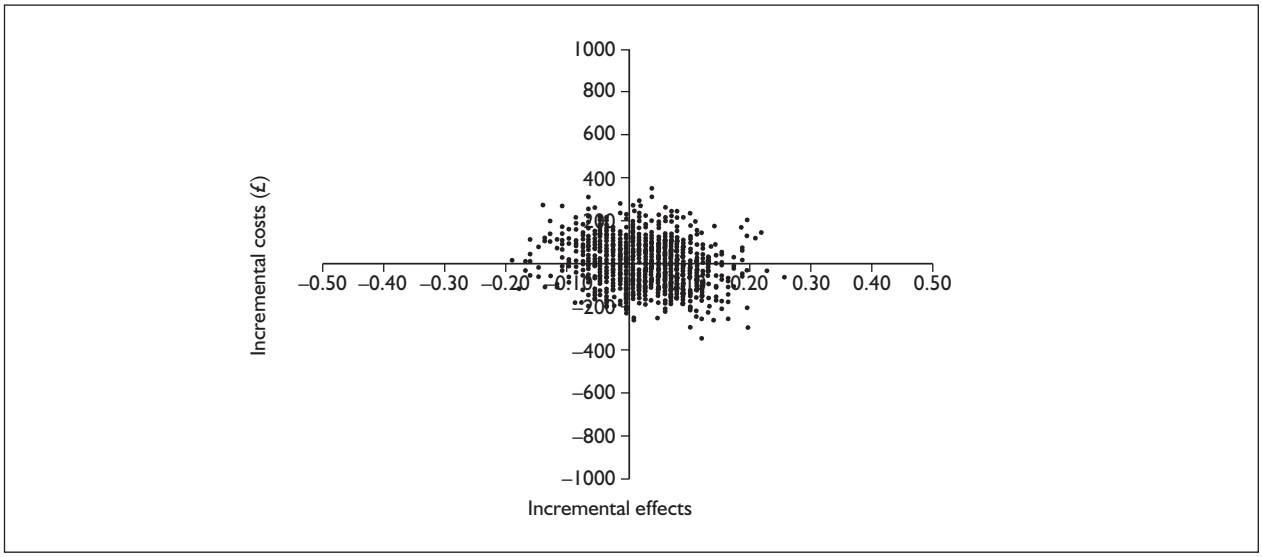

FIGURE 18b *Complete case analysis: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured based on 1000 bootstrap replicates. In this analysis, all children missing data on either costs or clinical outcomes were omitted from the analysis.*

Basing costs on data collected from the resource use questionnaire completed by parents (or guardians) 3 and 9 months after start of treatment (rather than using cost data collected in a retrospective review of patients' medical records) also had a substantial effect on cost-effectiveness (*Figure 18a,f*). Based on the questionnaires completed by parents (or guardians), the active treatment group within the trial was associated with substantially higher costs than the placebo group (£458 and £274 per child, respectively), although the difference in costs did not reach statistical significance on a two-tailed test, as there was a 4.06% chance that treatment would be less costly than placebo. Within this analysis, active treatment cost (on average) £5704 per case of OME cured and had a 64% chance of being cost-effective if the NHS were willing to pay £1000 per case cured.

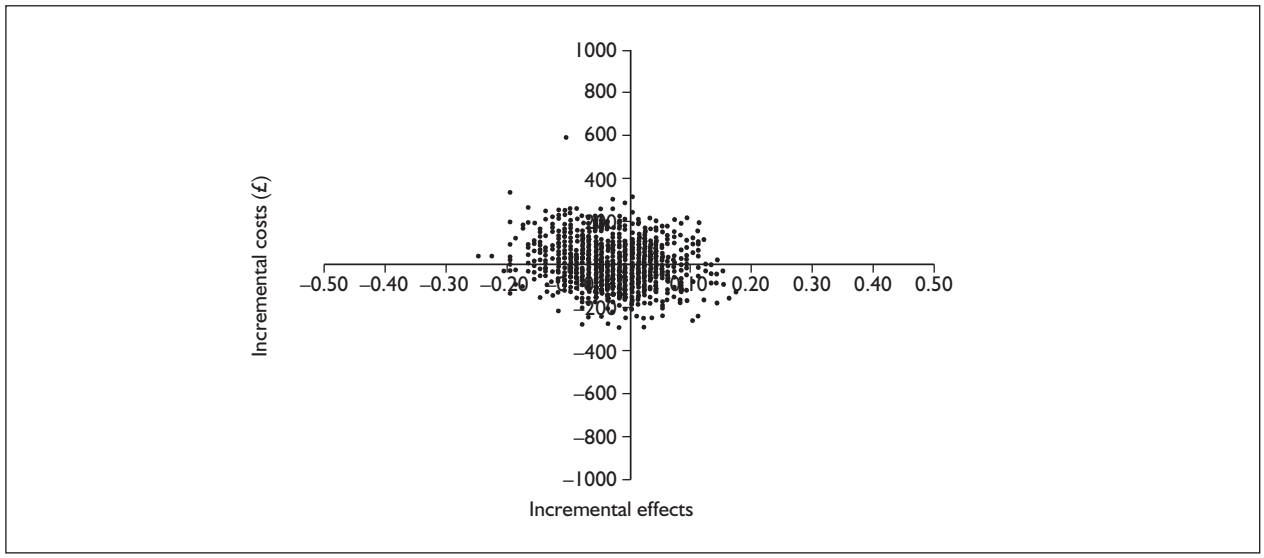

FIGURE 18c *Outcomes measured at 1 month: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured. In this analysis, data on the primary outcome measure were based on outcomes assessed 1 month after start of treatment. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

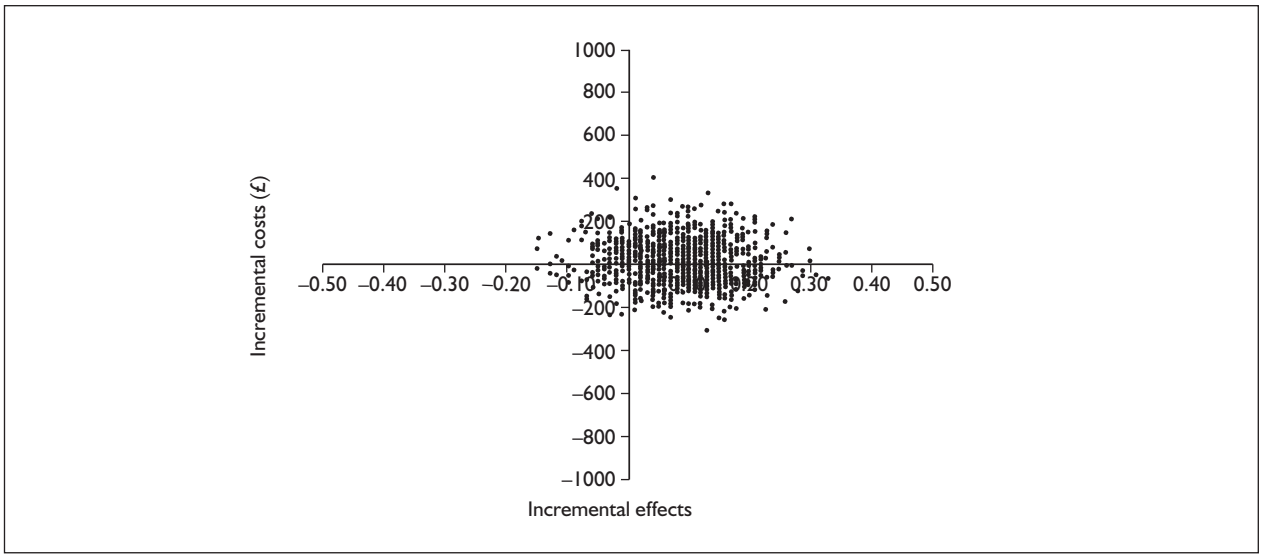

FIGURE 18d *Outcomes measured at 3 months: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured. In this analysis, data on the primary outcome measure were based on outcomes assessed 3 months after start of treatment. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

Subgroup analyses

In order to explore how incremental cost-effectiveness varies by characteristics of the children eligible for treatment, subgroup analysis was performed (*Table 31*). Subgroups investigated in such analyses comprised age, clinical severity, atopy, season, gender and with or without AM. *Figures 19* and *20* show the results of the subgroup analysis displayed graphically on cost-effectiveness planes and CEACs, while *Table 31* shows the cost and effect differences as well as the ICERs and the probabilities of the active treatment group being cost-effective in each subgroup.

The subgroup analysis found the results to be particularly sensitive to age, both in terms of costs and outcomes. In children aged 6.5 years and over, older children, the active treatment group

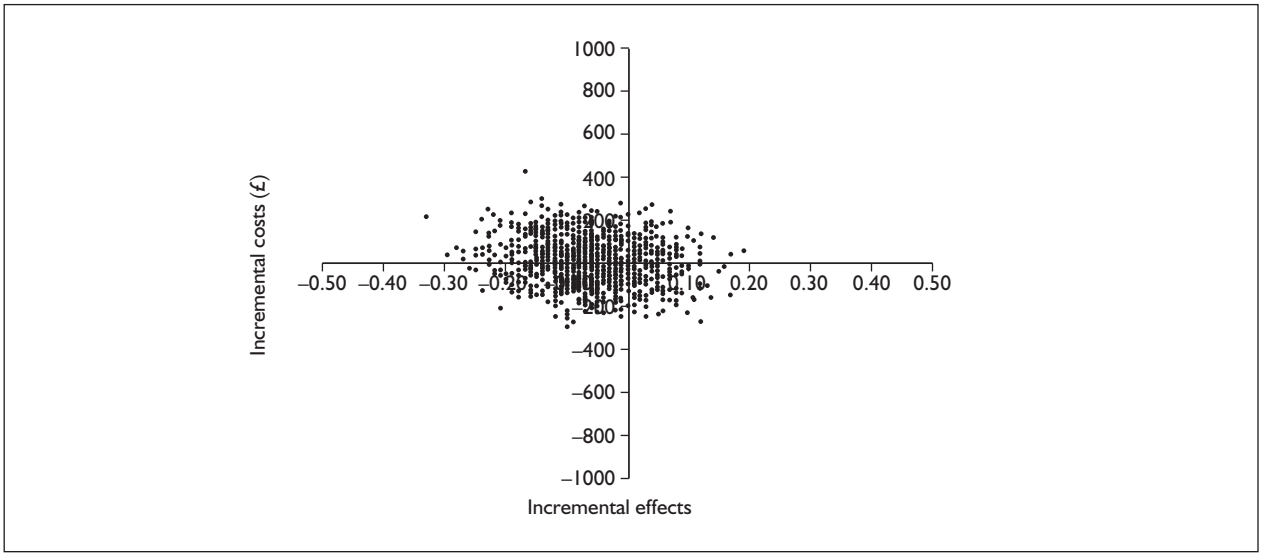

FIGURE 18e *Outcomes measured at 9 months: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured. In this analysis, data on the primary outcome measure were based on outcomes assessed 9 months after start of treatment. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

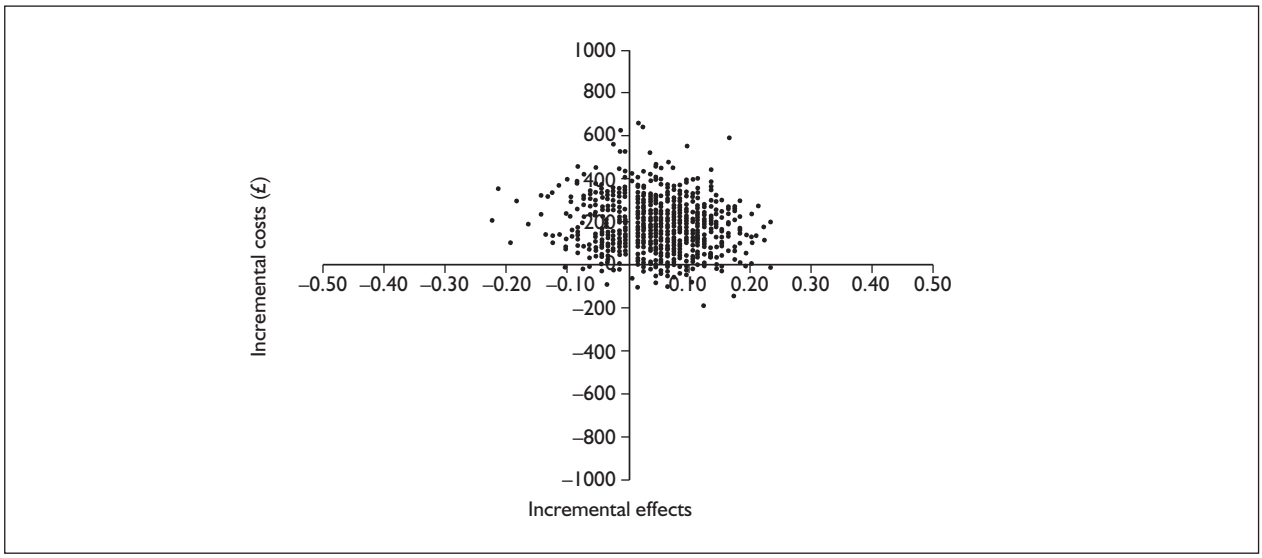

FIGURE 18f *Parental costs/resource use: cost-effectiveness plane showing the mean differences in costs and the proportion of children cured. In this analysis, data on costs were based on the resource use questionnaire completed by parents at 3 and 9 months after start of treatment. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

accrued lower NHS costs than the placebo group, suggesting that treatment would save an average of £152 per child. By contrast, in younger children aged between 4 and 6.5 years, the treatment group had higher costs than placebo by an average of £101, although the difference between treatment groups did not reach statistical significance in either subgroup. However, younger children accrued higher total health-care costs than older children regardless of which treatment they received.

Furthermore, the proportion of patients cured of OME by 1 or 3 months was significantly higher in the treatment group than for placebo in the subgroup of older children, in whom there was a 99% probability that treatment was more effective. Conversely, fewer patients were cured in the active treatment arm than in the placebo group in the subgroup in younger children, although the difference in this group did not reach statistical significance.

The marked differences in costs and benefits translated into substantial differences in cost-effectiveness. Treatment dominated placebo and had a 99.2% probability of being cost-effective at a £1000 per cure threshold in children aged 6.5 years and over, but had a 13.6% probability of being cost-effective in children aged between 4 and 6.49 years in whom the active treatment group was dominated by placebo (i.e. more costly and less effective). The difference in outcomes may reflect differences in compliance but more likely the probability of spontaneous recovery, while the difference in cost may reflect changes in the probability of undergoing surgery or be the result of the difference in clinical outcomes. However, further research is required to confirm or refute these hypotheses.

Marked differences were also observed between the early and later phases of the trial, which differed in a number of aspects described in Chapter 2, Changes to the original protocol – particularly in the use of AM. The active treatment group was dominant over placebo in the subgroup of children who were recruited with AM, being more effective and less costly, and there was a 74% probability that steroids were cost-effective at a £1000 per case cured ceiling ratio. By contrast, active treatment was more costly in the subgroup of children recruited under the amended protocol who did not have a period of AM and cost £1964 per QALY compared with placebo, with a 40% probability of being cost-effective among those children recruited without AM.

DOI: 10.3310/hta13370

TABLE 31 *Cost-effectiveness results for study population and by each subgroup category (pound sterling, 2006–7 prices). Except for the base-case analysis (which was based on 5000 bootstrap replicates for each of the five data sets), all results were based on 1000 bootstrap replicates for each of the five imputed data sets generated through multiple imputation*

	Total costs (95% CI)			Proportion of children cured (95% CI)				Probability that steroid arm is		Probability treatment cost-effective at ceiling ratio			Probability steroid arm is	
Type of analysis	**Active**	**Placebo**	**Difference**	**Active**	**Placebo**	**Difference**	**Cost/OME cured**	**Dominant**	**Dominated**	**£500**	**£1000**	**£2000**	**More effective**	**Less costly**
Base case (placebo $n = 112$; active treatment $n = 105$;)	£454 (£283 to £624)	£442 (£315 to £570)	£11 (–£199 to £222)	0.6324 (0.5383 to 0.7265)	0.6 (0.503 to 0.697)	0.0324 (–0.1032 to 0.168)	£347	34.89%	19.42%	51.86%	56.40%	61.01%	65.43%	46.28%
Subgroup analyses														
Younger children < 6.5 years (placebo $n = 74$; active treatment $n = 68$)	£559 (£321 to £797)	£458 (£305 to £611)	£101 (–£176 to £378)	0.5706 (0.4518 to 0.6894)	0.6622 (0.5517 to 0.7726)	–0.0916 (–0.2527 to 0.0696)	Dominated (–£1101)	4.56%	67.59%	16.96%	13.62%	11.06%	12.92%	24.04%
Older children ≥ 6.5 years (placebo $n = 38$; active treatment $n = 37$)	£260 (£117 to £402)	£412 (£223 to £600)	–£152 (–£380 to £77)	0.7459 (0.6016 to 0.8903)	0.4789 (0.302 to 0.6559)	0.267 (0.042 to 0.492)	Dominant (–£568)	90.22%	0.08%	98.28%	99.24%	99.54%	99.22%	90.92%
With atopy (placebo $n = 33$; active treatment $n = 35$)	£449 (£166 to £733)	£398 (£228 to £569)	£51 (–£260 to £362)	0.6457 (0.4845 to 0.8069)	0.7273 (0.5623 to 0.8922)	–0.0816 (–0.3161 to 0.153)	Dominated (–£624)	10.30%	48.48%	30.70%	26.22%	23.28%	22.68%	39.14%
Without atopy (placebo $n = 79$; active treatment $n = 70$)	£456 (£248 to £663)	£461 (£303 to £618)	–£5 (–£264 to £254)	0.6257 (0.5102 to 0.7412)	0.5468 (0.4321 to 0.6616)	0.0789 (–0.0866 to 0.2444)	Dominant (–£63)	46.18%	9.60%	62.98%	69.56%	76.34%	83.96%	52.62%
Boys (placebo $n = 63$; active treatment $n = 52$)	£527 (£269 to £784)	£465 (£297 to £632)	£62 (–£235 to £359)	0.6654 (0.5348 to 0.7959)	0.6286 (0.5095 to 0.7476)	0.0368 (–0.138 to 0.2116)	£1684	23.94%	24.98%	39.14%	44.26%	51.54%	65.08%	33.88%
Girls (placebo $n = 49$; active treatment $n = 53$)	£382 (£164 to £600)	£414 (£237 to £590)	–£32 (–£315 to £251)	0.6 (0.4662 to 0.7338)	0.5663 (0.4226 to 0.7099)	0.0337 (–0.1628 to 0.2303)	Dominant (–£942)	39.82%	19.42%	61.74%	62.62%	63.46%	61.24%	58.10%

continued

TABLE 31 *Cost-effectiveness results for study population and by each subgroup category (pound sterling, 2006–7 prices). Except for the base-case analysis (which was based on 5000 bootstrap replicates for each of the five data sets), all results were based on 1000 bootstrap replicates for each of the five imputed data sets generated through multiple imputation (continued)*

	Total costs (95% CI)			Proportion of children cured (95% CI)				Probability that steroid arm is		Probability treatment cost-effective at ceiling ratio			Probability steroid arm is	
Type of analysis	Active	Placebo	Difference	Active	Placebo	Difference	Cost/OME cured	Dominant	Dominated	£500	£1000	£2000	More effective	Less costly
With AM (placebo $n = 37$; active treatment $n = 35$)	£417 (£125 to £710)	£566 (£330 to £803)	–£149 (–£530 to £232)	0.5143 (0.3482 to 0.6804)	0.5081 (0.3403 to 0.676)	0.0062 (–0.2298 to 0.2422)	Dominant (–£24,126)	43.02%	12.26%	76.56%	73.92%	68.16%	51.94%	78.82%
Without AM (placebo $n = 75$; active treatment $n = 70$)	£472 (£268 to £675)	£381 (£246 to £516)	£91 (–£148 to £329)	0.6914 (0.5806 to 0.8023)	0.6453 (0.5355 to 0.7552)	0.0461 (–0.1118 to 0.204)	£1964	18.77%	22.59%	31.42%	39.88%	51.14%	72.94%	23.02%
Severe[a] (placebo $n = 23$; active treatment $n = 23$)	£586 (£240 to £932)	£442 (£219 to £664)	£145 (–£270 to £560)	0.4261 (0.2219 to 0.6302)	0.4696 (0.2605 to 0.6786)	–0.0435 (–0.3371 to 0.2501)	Dominated (–£3331)	10.36%	47.32%	24.12%	24.60%	27.54%	33.36%	25.52%
Non severe[a] (placebo $n = 75$; active treatment $n = 65$)	£367 (£165 to £568)	£460 (£301 to £618)	–£93 (–£352 to £166)	0.7138 (0.6031 to 0.8246)	0.6613 (0.5491 to 0.7735)	0.0525 (–0.1013 to 0.2063)	Dominant (–£1771)	58.71%	8.17%	79.88%	81.28%	81.40%	74.02%	76.44%
Seasons: January–March (placebo $n = 44$; active treatment $n = 42$)	£451 (£208 to £694)	£326 (£206 to £445)	£125 (–£149 to £399)	0.6524 (0.5043 to 0.8005)	0.7409 (0.6081 to 0.8737)	–0.0885 (–0.2887 to 0.1116)	Dominated (–£1411)	5.22%	67.76%	14.26%	13.08%	12.98%	19.10%	18.36%
Seasons: April–December (placebo $n = 68$; active treatment $n = 63$)	£456 (£229 to £682)	£518 (£335 to £701)	–£62 (–£352 to £228)	0.619 (0.4943 to 0.7438)	0.5088 (0.3851 to 0.6326)	0.1102 (–0.0665 to 0.287)	Dominant (–£565)	60.56%	4.02%	77.84%	83.76%	88.60%	89.06%	67.48%

a Severe disease was defined as a clinical severity score above 0.62 (the upper quartile limit of the sample). Clinical severity was defined as the first principal component of the baseline variables – frequency of surgery attendance in last 12 months for ear problems; tympanogram readings; age at first episode of hearing infection/problem; total reported episodes of ear problems over last 12 months; RESP score – identified in an analysis of these variables ignoring randomisation group.

FIGURES 19a–l *Cost-effectiveness planes showing the mean differences in costs and in the primary outcome measure from the trial data. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

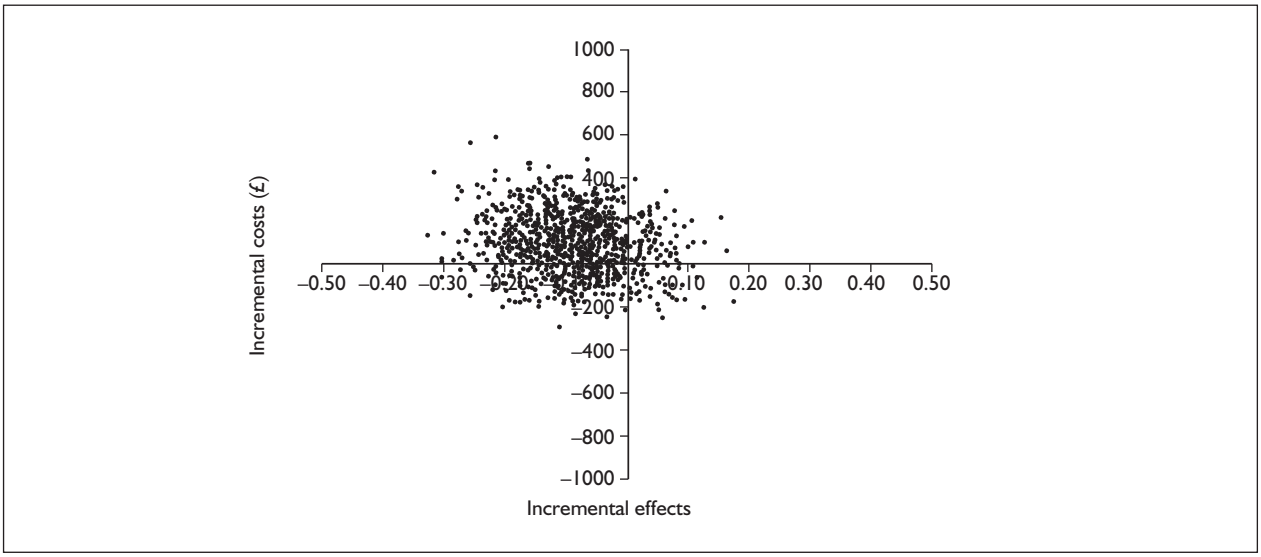

FIGURE 19a *Younger children (< 6.5 years at baseline): scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

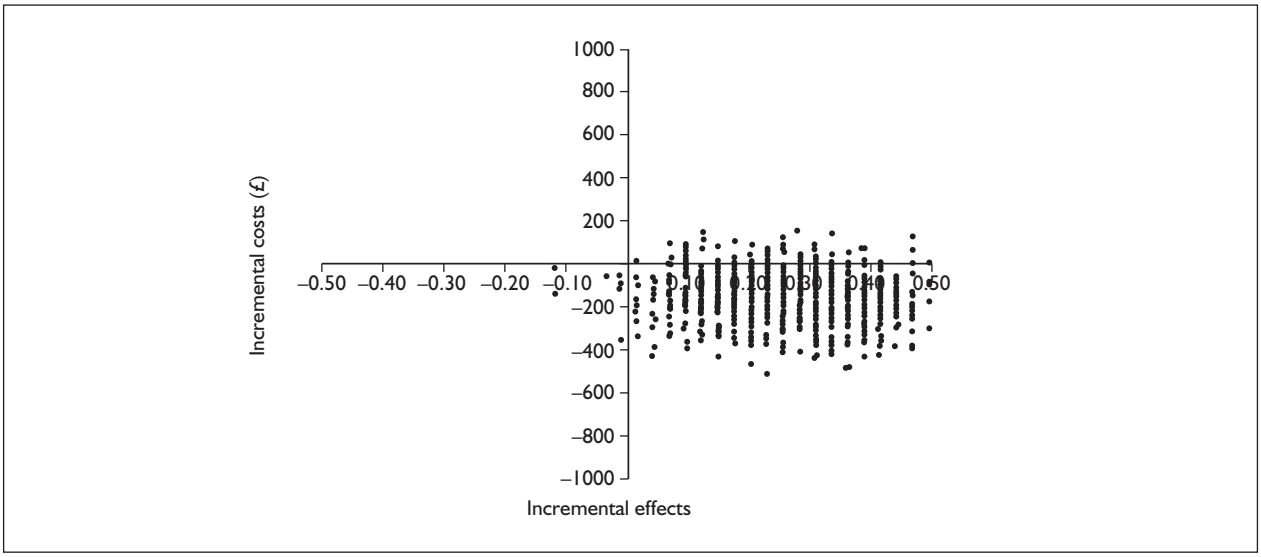

FIGURE 19b *Older children (≥6.5 years at baseline): scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

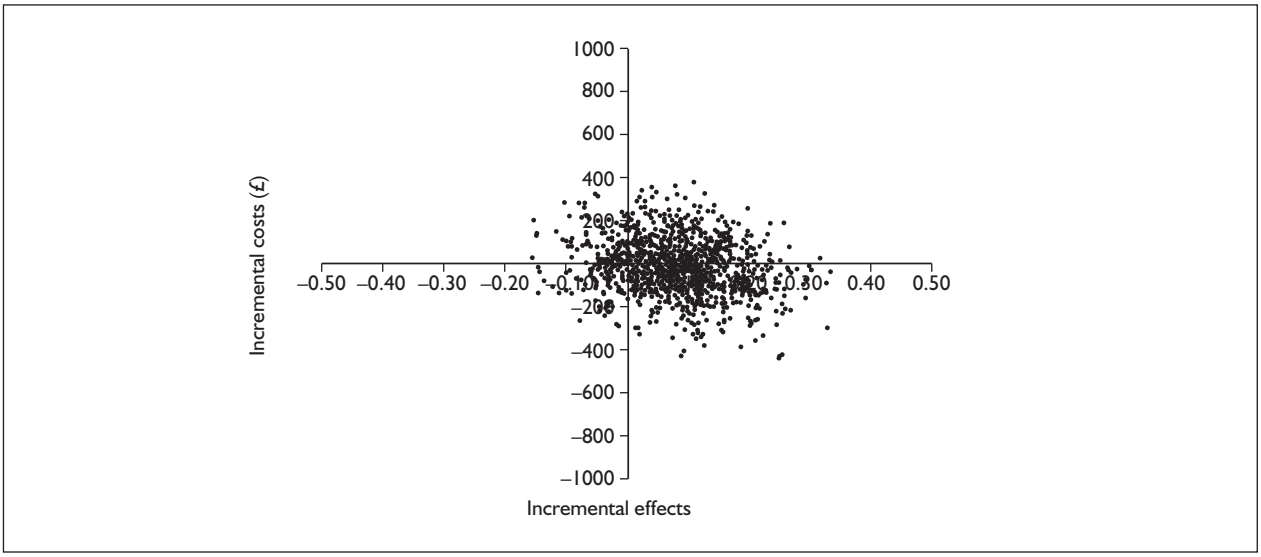

FIGURE 19c *Children without atopy: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

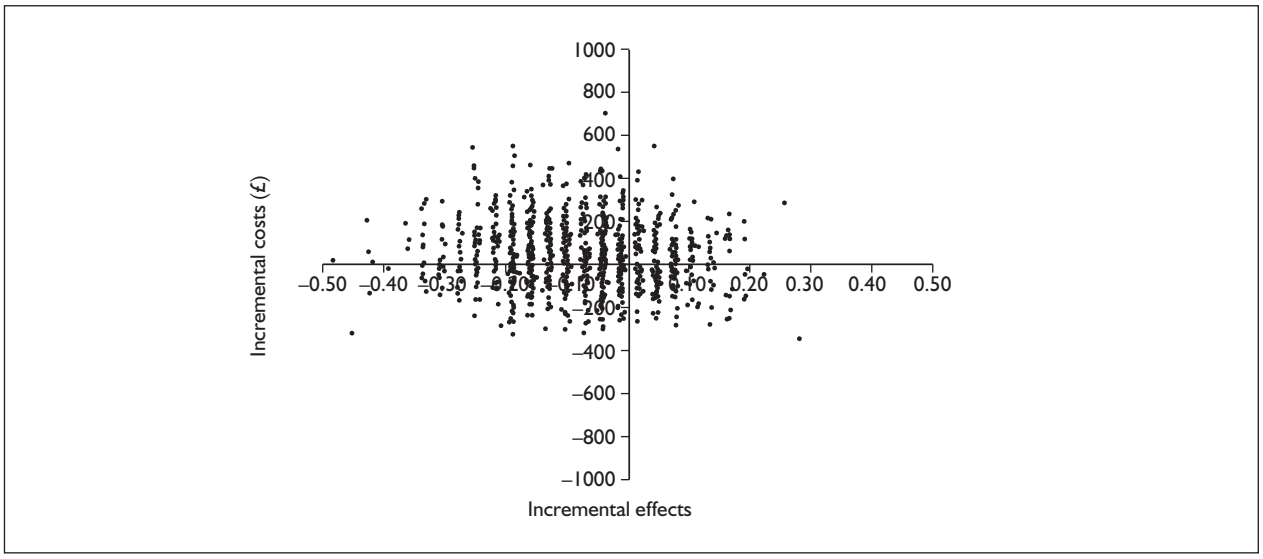

FIGURE 19d *Children with atopy: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

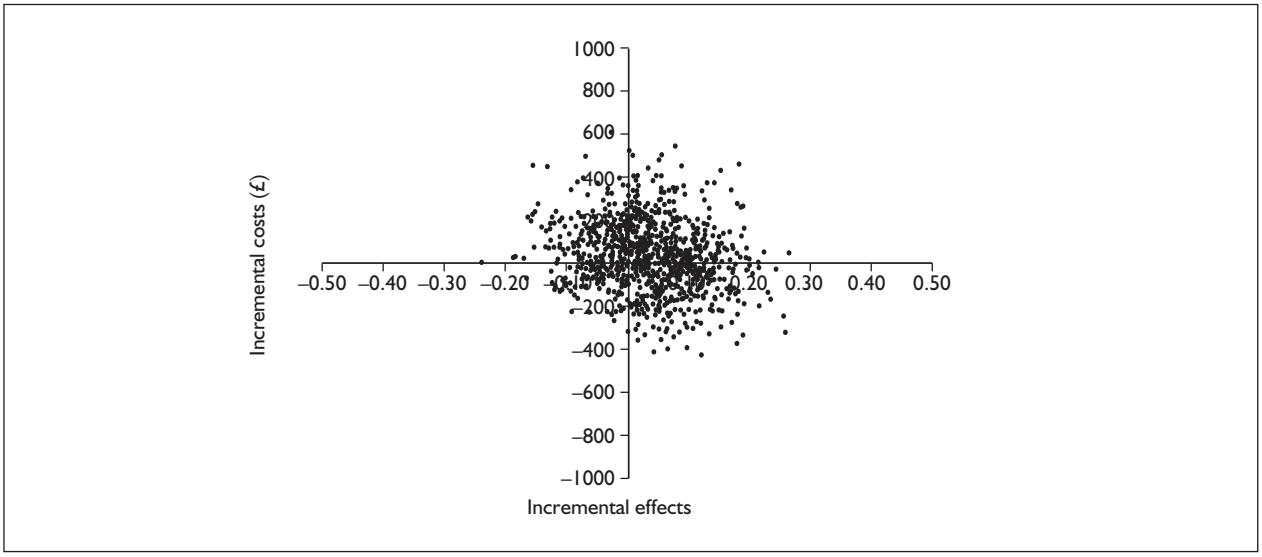

FIGURE 19e *Boys: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

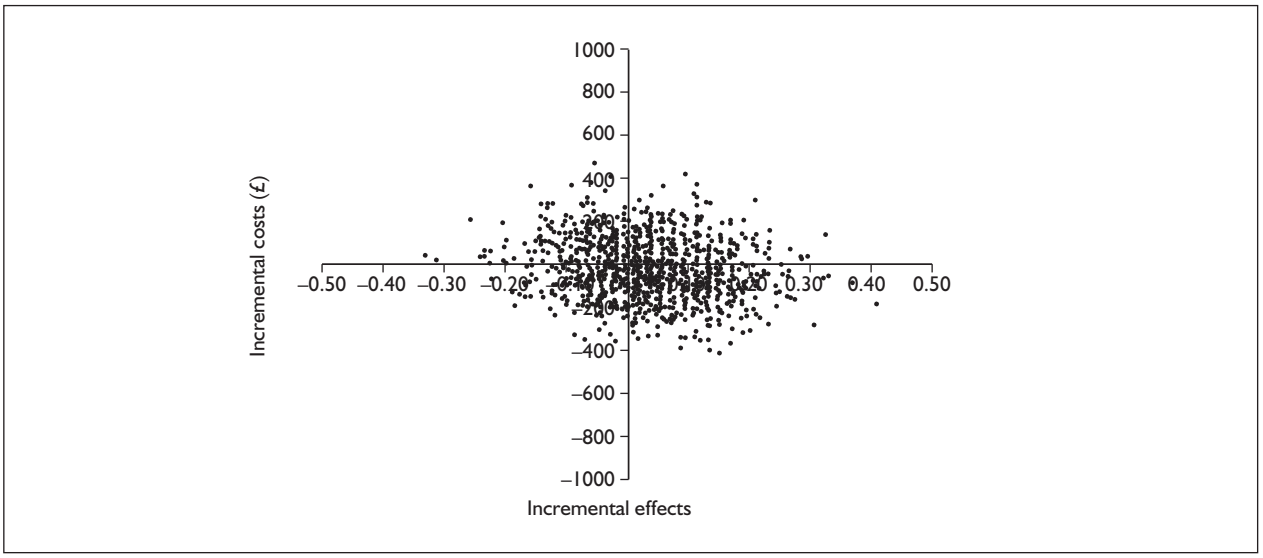

FIGURE 19f *Girls: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

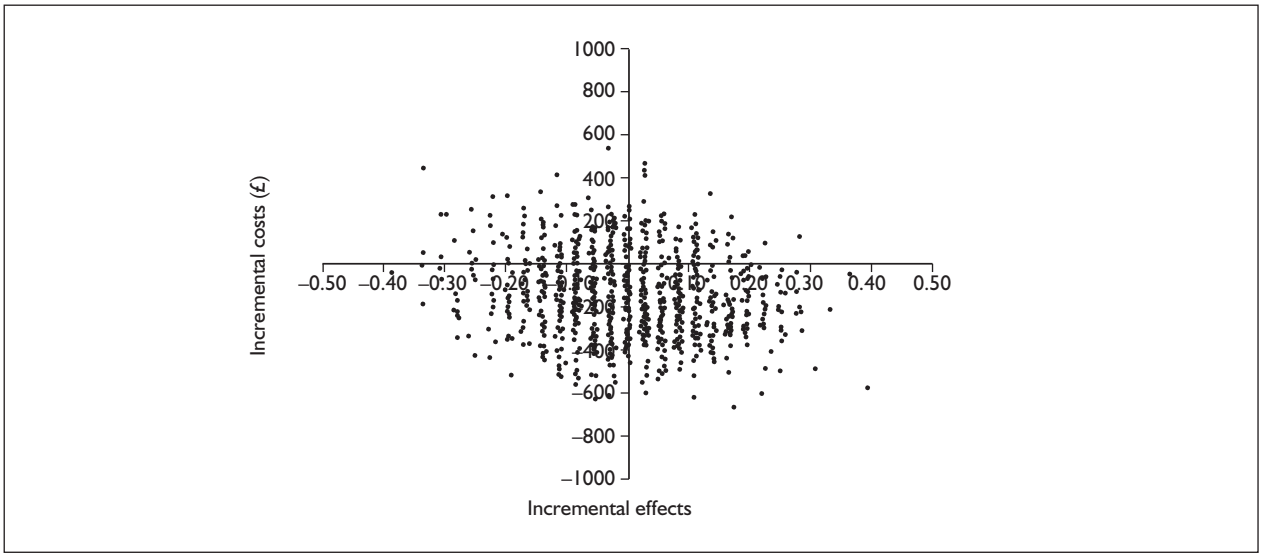

FIGURE 19g *Children recruited with AM: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

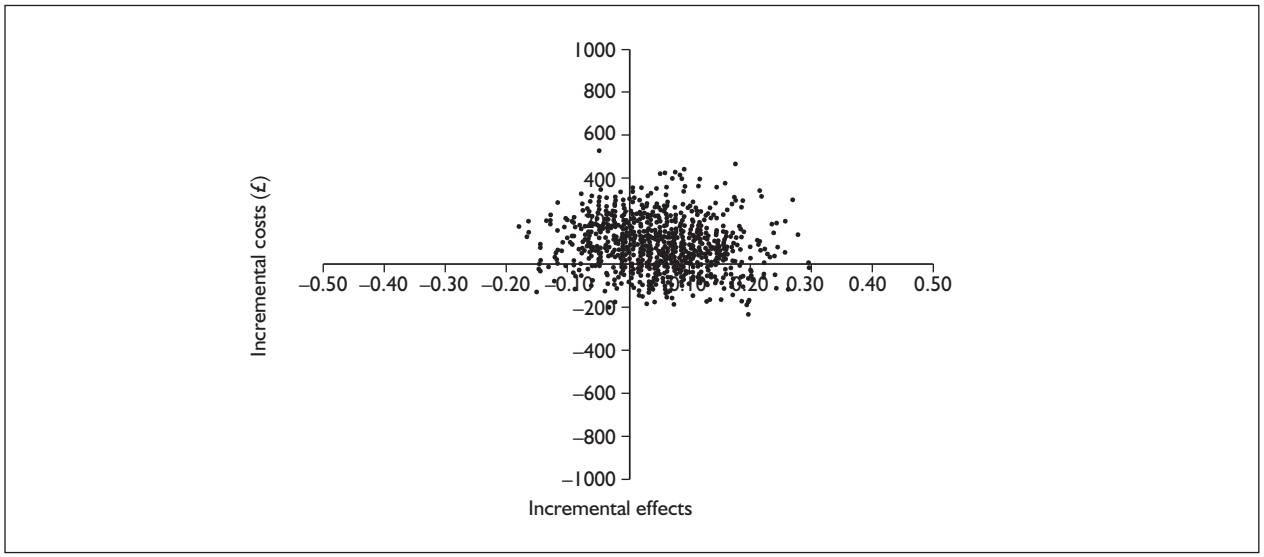

FIGURE 19h *Children recruited without AM: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

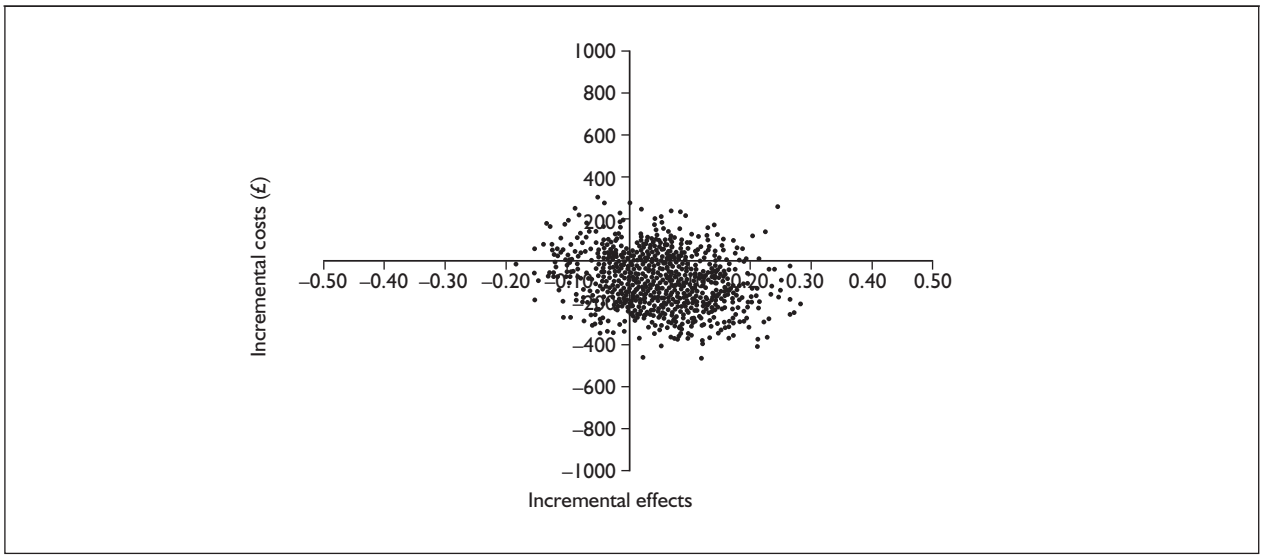

FIGURE 19i *Children with non-severe disease: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. Severe disease was defined as a clinical severity score above 0.62 (the upper quartile limit of the sample). Clinical severity was defined as the first principal component of the baseline variables – frequency of surgery attendance in the last 12 months for ear problems; tympanogram readings; age at first episode of hearing infection/problem; total reported episodes of ear problems over last 12 months; RESP score – identified in an analysis of these variables ignoring randomisation group.*

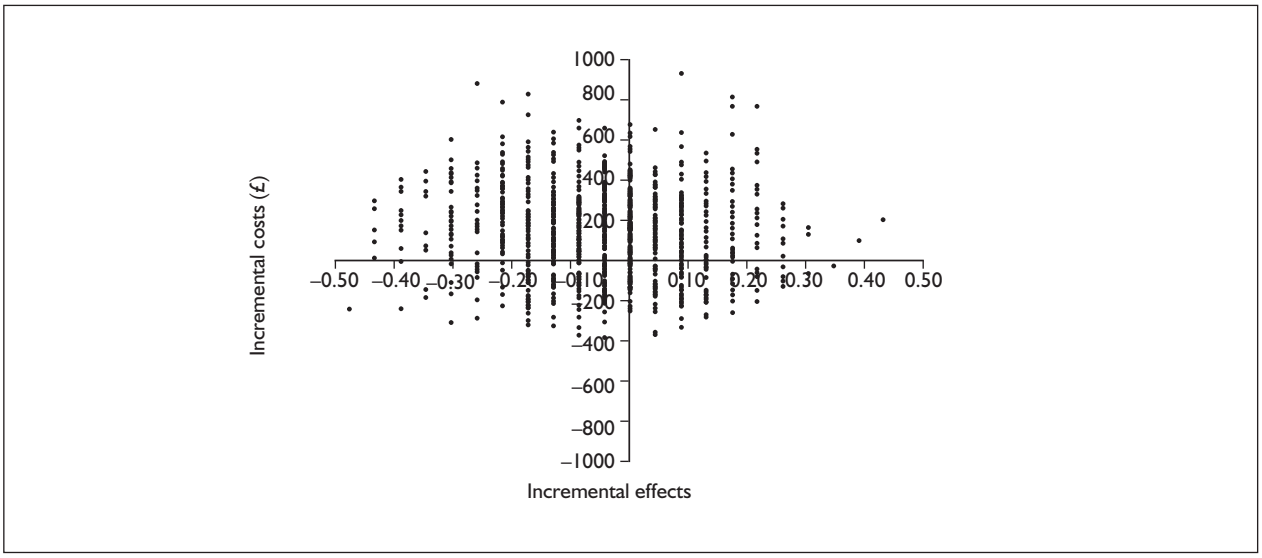

FIGURE 19j *Children with severe disease: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

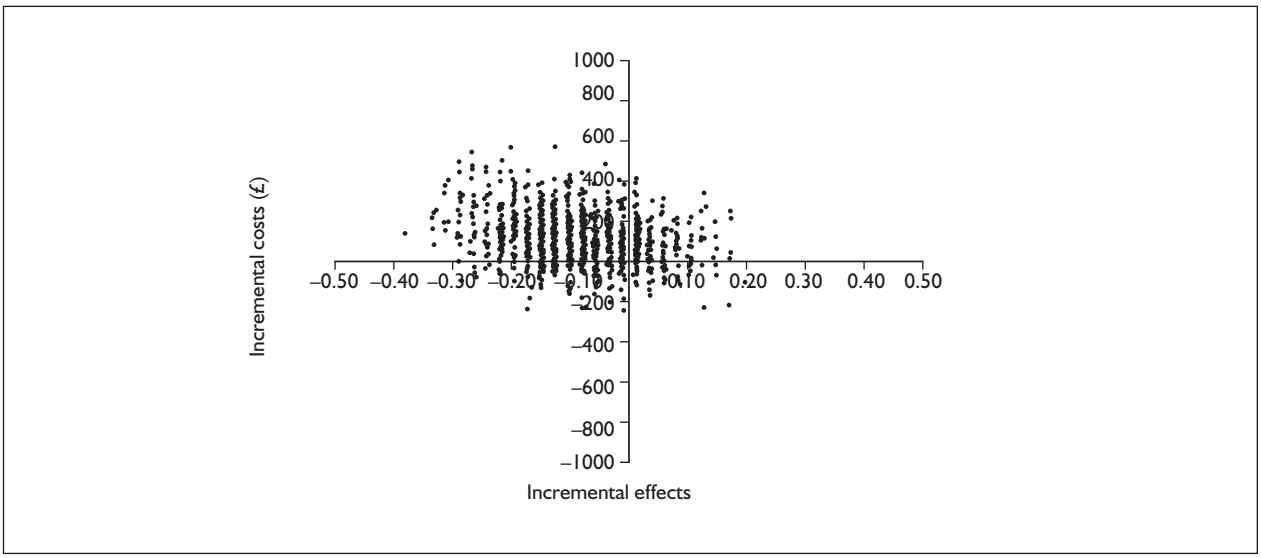

FIGURE 19k *Children recruited during January, February and March: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

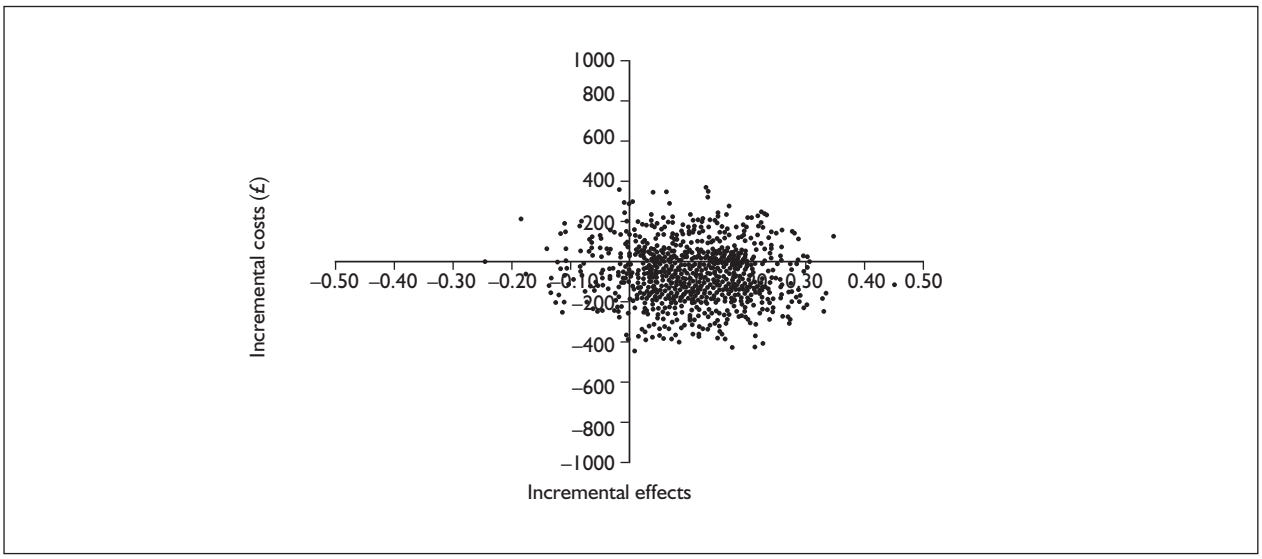

FIGURE 19I *Children recruited between April and December: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

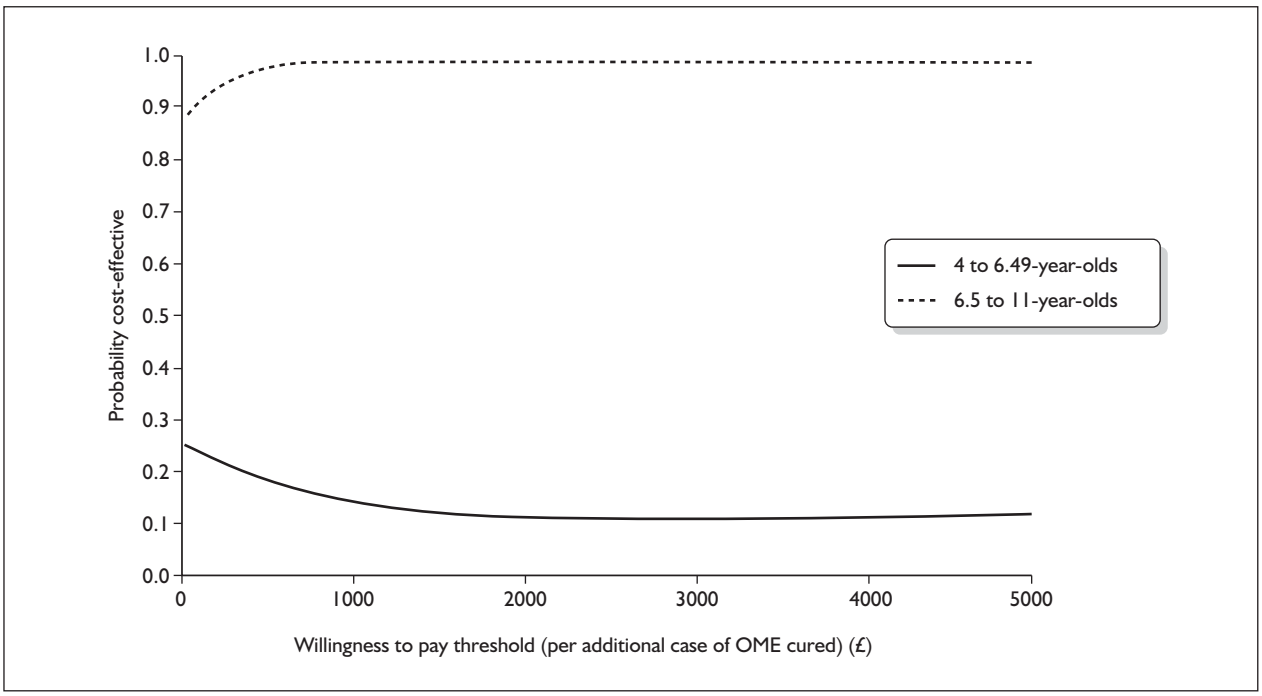

FIGURE 20a *CEACs for different age subgroups. Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME. All analyses are based on 1000 bootstrap replicates for each of the five imputed data sets generated in multiple imputation.*

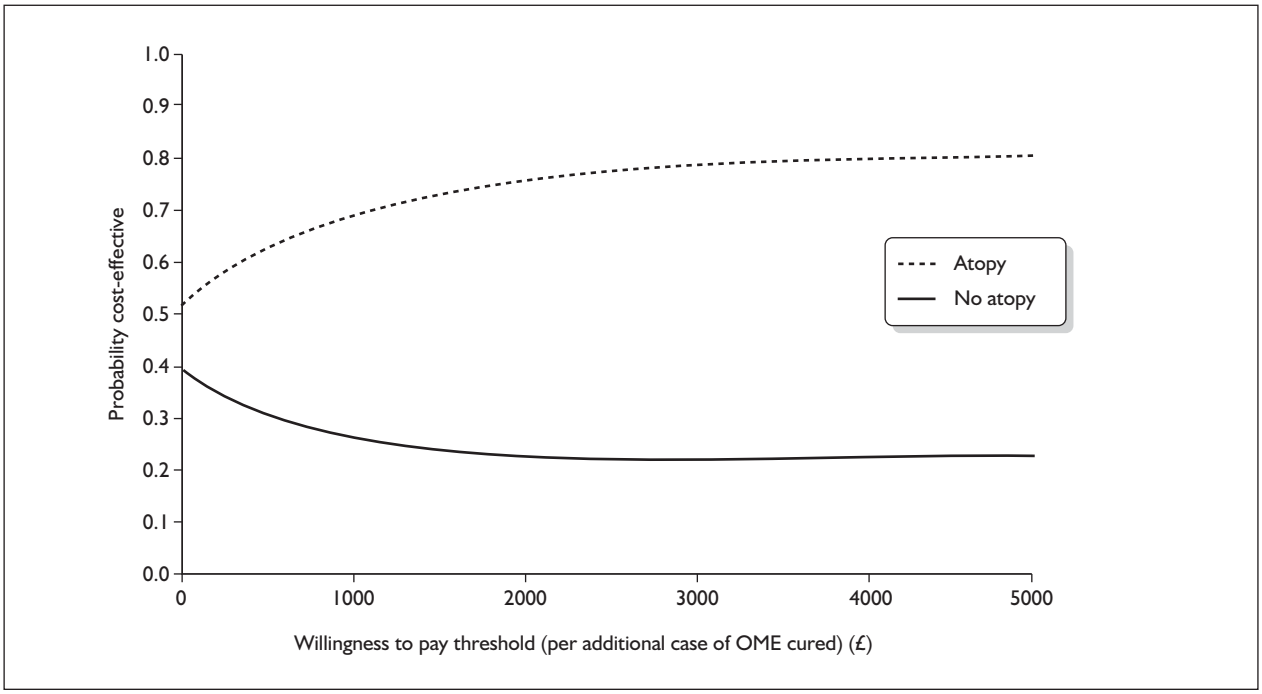

FIGURE 20b *CEACs for different atopy subgroups. Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME. All analyses are based on 1000 bootstrap replicates.*

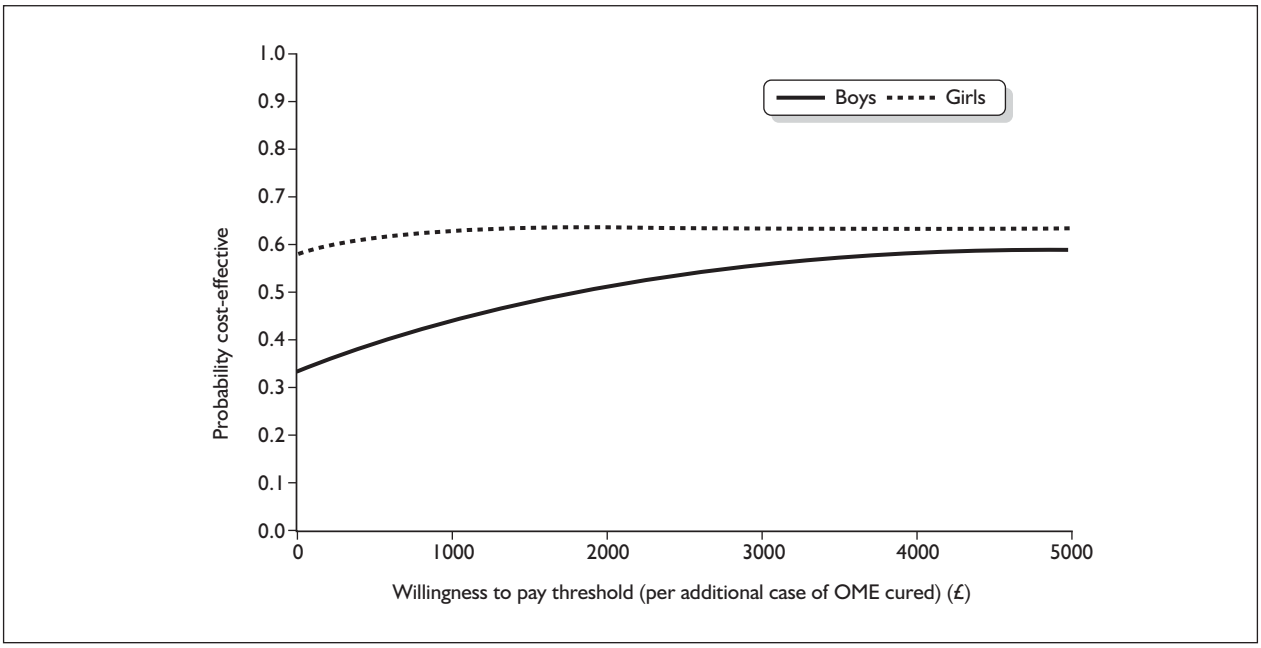

FIGURE 20c *CEACs for different gender subgroups. Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME. All analyses are based on 1000 bootstrap replicates.*

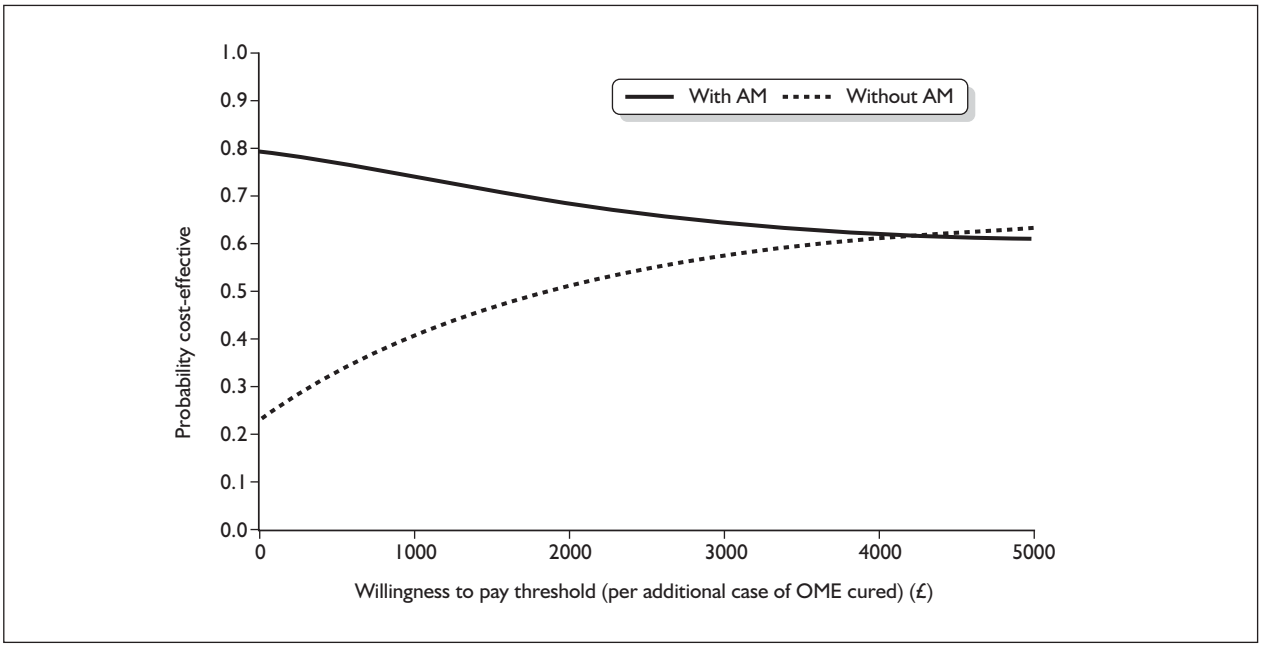

FIGURE 20d *CEACs for different trial subgroups (with and without AM). Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME. All analyses are based on 1000 bootstrap replicates.*

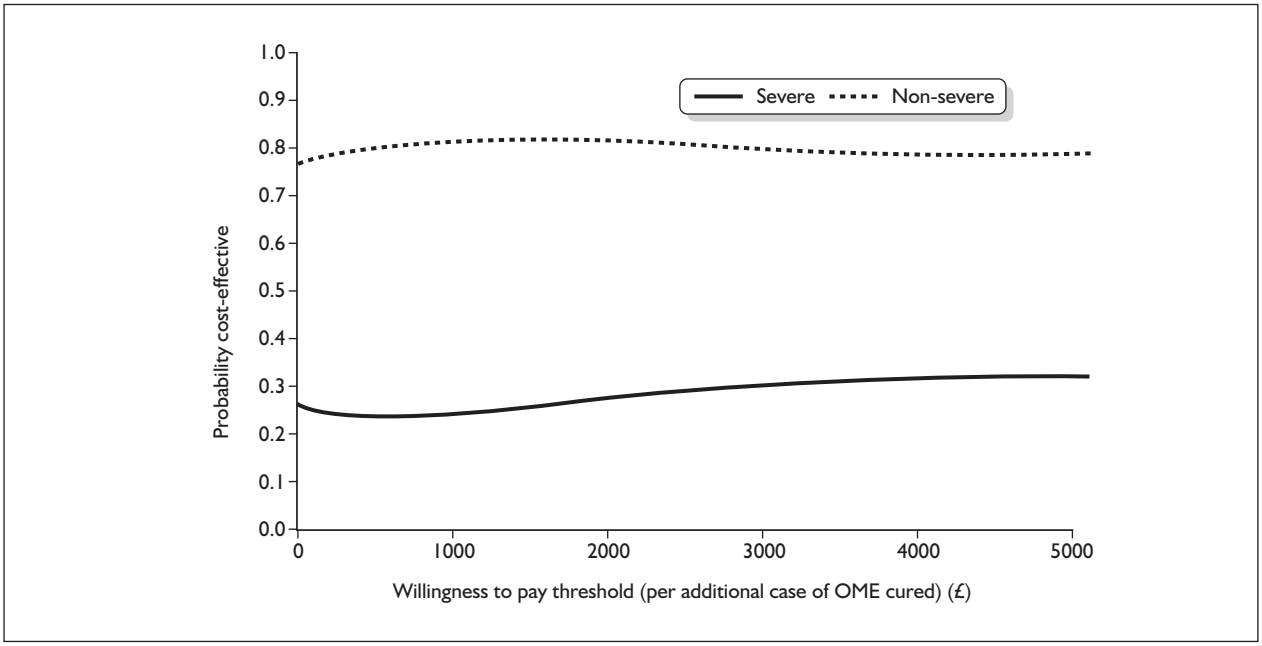

FIGURE 20e *CEACs for different severity subgroups. Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME. All analyses are based on 1000 bootstrap replicates.*

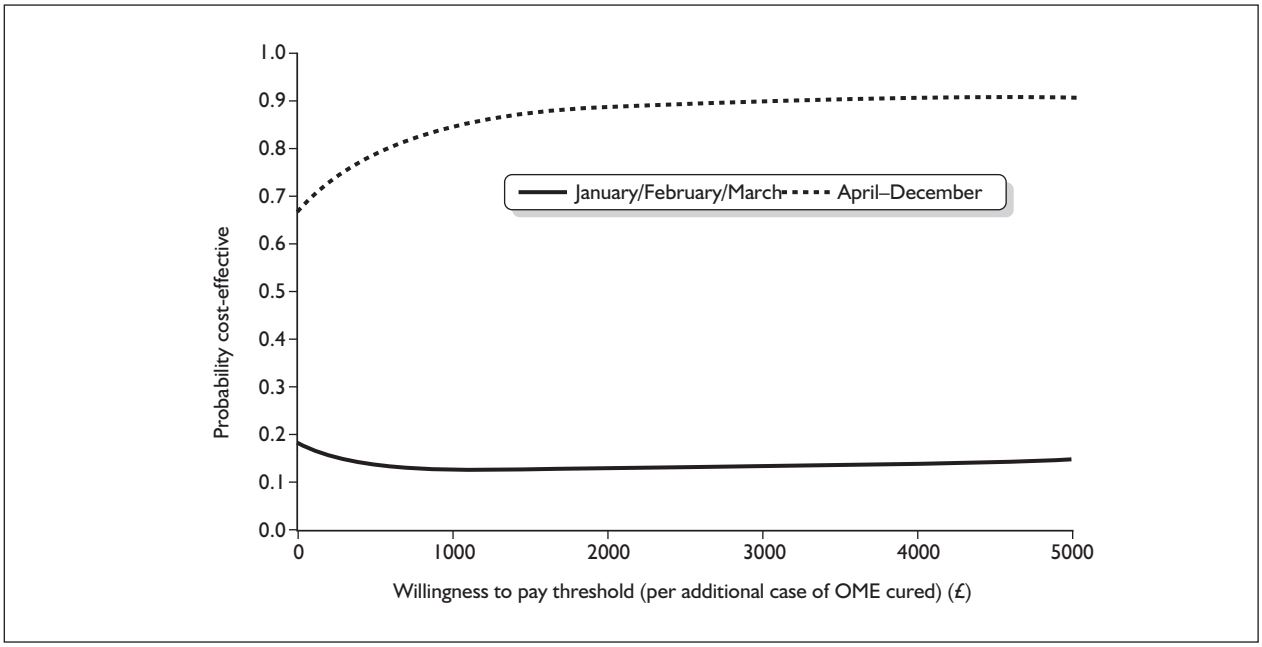

FIGURE 20f *CEACs for different season subgroups. Each curve shows how the probability that intranasal steroids are cost-effective varies with changes in the amount that society is willing to pay to cure one case of OME. All analyses are based on 1000 bootstrap replicates.*

Results of the cost–utility analysis

Base case

The incremental costs calculated for the CUA are the same as those for the CEA, as the same cost data were used. However, whereas the CEA suggests that there was a non-significant trend towards better outcomes in the intranasal steroid arm of the trial than in the placebo group, the CUA observes a non-significant trend towards worse outcomes with active treatment. As described above (see *Table 29*), the active treatment group accrued an average of 0.0166 fewer QALYs per child than the placebo group. There was found to be a 24% probability that intranasal steroids are more effective than placebo in terms of the QALYs accrued over the 9-month trial period, which means that there was no significant difference between study arms in terms of the number of QALYs accrued ($p = 0.24$ on a one-tailed test). The base-case analysis therefore suggests that steroid treatment is dominated by placebo, being more costly and less effective. This finding differs from the CEA, which found active treatment to cost £347 per QALY gained, as a higher proportion of children in the active treatment group achieved tympanometric cure at 1 or 3 months (than those in the placebo group) despite having lower QoL.

However, there is a very large degree of uncertainty around the findings of both analyses (see *Figures 15*, *16* and *21* and *Tables 30* and *32*). The scattergraph showing the distribution of incremental costs and benefits for the CUA shows that the true incremental cost per QALY gained could fall into any of the four quadrants on the cost-effectiveness plane (see *Figure 21b*). There is a 12% chance that steroid treatment is more costly and more effective (falling into the top-right quadrant of the cost-effectiveness plane), a 12% chance that it is dominant over placebo (i.e. less costly and more effective), a 42% chance that steroids are dominated by placebo (i.e. more costly and less effective) and a 34% chance steroids are less costly and less effective (see *Figure 21b*).

If society is willing to pay £20,000 to gain an additional QALY, there is a 24% chance that steroids are a cost-effective use of NHS resources (see *Figure 21a*); given that most of the bootstrap replicates found active treatment to be less effective than placebo, the probability that treatment was cost-effective fell as the ceiling ratio increased.

As for the CEA, the base-case CUA included imputation of missing data for both costs and utilities using multiple imputation techniques (see Chapter 2, Methods for dealing with missing data).

Imputation was particularly influential for utility data, as 62% (134/217) of children were missing HUI3 utility data for at least one time point. Due to the substantial amount of missing utility data, uncertainty about the correct value for data points that had been imputed accounted for 28.0% of the total variance around the mean incremental QALY gain from treatment, but accounted for just 2.3% of the variance around the mean incremental cost.

Sensitivity analyses

A number of sensitivity analyses were conducted in order to assess the impact of the assumptions and decisions about analytical methods used in the base-case analysis. The first set of analyses assessed the results that would be obtained if the two alternative utility instruments used in the study were used in place of HUI3. This analysis showed that the choice of utility instrument has a large effect on the probability that intranasal steroids are more effective than placebo, the probability that treatment is cost-effective (*Figure 22*) and the point estimates for the ICER (see *Table 32*).

When the HUI2 questionnaire was used, the active treatment group accrued more QALYs than placebo (not significant) and there was a 66% chance that active treatment would produce more QALYs than placebo (compared with 24% in the base-case analysis). Furthermore, active treatment cost £2161 per QALY gained and had a 63% chance of being cost-effective relative to placebo at a £20,000 per QALY threshold (see *Figures 22a,b*).

Using the EQ-$5D_5$ questionnaire increased estimates of the incremental benefits of treatment still further, such that intranasal steroids had an 89% chance of being more effective than placebo and cost £418 per QALY gained with an 89% chance of being cost-effective at a £20,000 per QALY ceiling ratio (see *Figures 22a,b*).

The second set of sensitivity analyses conducted explored the impact of adjusting for baseline utility. For simplicity, such analyses were conducted using only the HUI3 instrument. When no adjustment was made for baseline utility, the absolute difference in QALYs between the two groups increased from 0.0166 to 0.0225 and the probability of active treatment being more effective than placebo fell to 11%. The probability of treatment being cost-effective at a £20,000 per QALY ceiling ratio fell to 12% (*Figure 23a,b*).

Thirdly, alternative methods for dealing with missing data were investigated. The complete case analysis assessed outcomes for the 104 out of 217 children who had full data on costs and for whom the HUI3 questionnaire was fully completed at all three time points (*Figures 24a,b*). Among this subgroup of children, costs were substantially higher in the active treatment group (£550 per child) and lower in the placebo group (£352 per child), although the absolute difference in QALYs between the two groups was reduced to 0.0059. However, the probability that treatment was cost-effective at a £20,000 per QALY ceiling ratio was similar to the base case at 25%.

We also investigated the impact of imputing missing utility data using the mapping equations produced in the analysis mapping between OM8-30 scores and HUI3 utilities (Appendix 15) instead of imputing both costs and utilities using multiple imputation. In these analyses, children who were missing HUI3 utility data at any given time point but for whom full information on predicted HL and all OM–30 facets or domains were available were assumed to have the utility that would be predicted based on the ordinary least-squares domain or facet-level model shown in Appendix 15. Linear interpolation/extrapolation was used to estimate QALYs for children who were missing mapped or observed utility data at either 3 or 9 months (see *Figure 2*), although no other imputation was used to estimate utility data that were missing after mapped values had been included. Similarly, the costs included in this analysis included only those costs observed directly in the trial, rather than values estimated using multiple imputation. As this comprised a sensitivity analysis, uncertainty around children's predicted utility was not taken into account within bootstrapping.

When the analysis was restricted to those children (154 out of 217 children) who had complete cost data and utility data at baseline and at one or more follow-up time points (obtained from either direct completion of HUI3 or OM8-30 mapping), the average cost was £475 per child in the active treatment group, compared with £376 per child in the placebo group (*Table 32*). However, as in the base-case analysis, there was no statistically significant difference in costs between the two groups. The difference in costs between this analysis and the base-case analysis is due to the different populations of children included in each

TABLE 32 *CUA results for base-case analysis, sensitivity analyses and subgroup analyses*

	Total costs (95% CI)			QALYs gained relative to baseline utility (95% CI)				Probability that active treatment is		Probability active treatment cost-effective at ceiling ratio			Probability that active treatment is	
Subgroup/ sensitivity analysis	**Active**	**Placebo**	**Difference**	**Active**	**Placebo**	**Difference**	**Cost/QALY**	**Dominant**	**Dominated**	**£20,000**	**£30,000**	**£50,000**	**More effective**	**Less costly**
Base case (placebo *n* = 112; active treatment *n* = 105; 5000 bootstrap replicates for each of five data sets)	£454 (£284 to £623)	£442 (£314 to £571)	£11 (–£199 to £222)	0.0361 (–0.0014 to 0.0736)	0.0527 (0.019 to 0.0864)	–0.0166 (–0.0652 to 0.032)	Dominated (–£676)	12.35%	42.29%	24.19%	23.92%	23.83%	23.82%	46.25%
Sensitivity analyses														
HUI2 (placebo *n* = 112; active treatment *n* = 105; 1000 bootstrap replicates for each of five data sets)	£454 (£287 to £620)	£442 (£315 to £570)	£11 (–£197 to £219)	0.0329 (0.0082 to 0.0577)	0.0277 (–0.0083 to 0.0638)	0.0052 (–0.0276 to 0.038)	£2161	31.91%	19.00%	63.20%	64.00%	64.68%	65.72%	47.16%
EQ-5D (placebo *n* = 112; active treatment *n* = 105; 1000 bootstrap replicates for each of five data sets)	£454 (£284 to £623)	£442 (£317 to £568)	£11 (–£199 to £222)	0.0305 (–0.0176 to 0.0787)	0.0037 (–0.0225 to 0.0298)	0.0268 (–0.0189 to 0.0726)	£418	41.98%	5.88%	88.66%	89.02%	89.22%	89.22%	46.88%
No adjustment for baseline utilities (placebo *n* = 112; active treatment *n* = 105; 1000 bootstrap replicates for each of five data sets)	£454 (£282 to £625)	£442 (£314 to £570)	£11 (–£199 to £221)	0.6045 (0.5244 to 0.6845)[a]	0.627 (0.5518 to 0.7021)[a]	–0.0225 (–0.0599 to 0.0149)[a]	Dominated (–£499)	5.94%	48.98%	11.64%	11.10%	10.56%	10.28%	46.68%
Complete case analysis (placebo *n* = 52; active treatment *n* = 52; 1000 bootstrap replicates for a single data set that excludes missing values)	£550 (£300 to £801)	£352 (£190 to £513)	£199 (–£99 to £497)	0.041 (0.011 to 0.072)	0.047 (0.016 to 0.079)	–0.0059 (–0.0501 to 0.0383)	Dominated (–£33,504)	4.50%	54.75%	25.30%	29.20%	32.20%	40.20%	9.50%

DOI: 10.3310/hta13370

Subgroup/ sensitivity analysis	Total costs (95% CI)			QALYs gained relative to baseline utility (95% CI)			Cost/QALY	Probability that active treatment is		Probability active treatment cost-effective at ceiling ratio			Probability that active treatment is	
	Active	Placebo	Difference	Active	Placebo	Difference		Dominant	Dominated	£20,000	£30,000	£50,000	More effective	Less costly
Mapped utilities using HUI3 facet model (placebo $n = 74$; active treatment $n = 80$; 1000 bootstrap replicates for a single data set that excludes missing values)	£475 (£290 to £660)	£376 (£240 to £511)	£100 (–£130 to £329)	0.041 (0.019 to 0.063)	0.041 (0.017 to 0.065)	–0.0003 (–0.033 to 0.0324)	Dominated (£–306,940)	12.20%	39.70%	39.10%	43.10%	45.80%	51.60%	20.90%
Mapped utilities using domain model (placebo $n = 74$; active treatment $n = 80$; 1000 bootstrap replicates for a single data set that excludes missing values)	£475 (£290 to £660)	£376 (£240 to £511)	£100 (–£130 to £329)	0.036 (0.014 to 0.058)	0.036 (0.012 to 0.061)	–0.0002 (–0.0329 to 0.0326)	Dominated (–£639,701)	11.30%	42.20%	39.30%	42.10%	45.40%	50.40%	18.70%
Parents' resource use questionnaire (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for each of five data sets)	£458 (£253 to £663)	£274 (£149 to £398)	£185 (–£69 to £438)	0.0361 (–0.0021 to 0.0743)	0.0527 (0.0187 to 0.0868)	–0.0166 (–0.0653 to 0.0321)	Dominated (–£11,115)	1.22%	72.27%	14.08%	16.92%	19.74%	24.22%	4.72%
Including tympanometry (placebo $n = 112$; active treatment $n = 105$; 1000 bootstrap replicates for each of five data sets)	£472 (£307 to £638)	£461 (£334 to £588)	£11 (–£196 to £219)	0.0361 (–0.0017 to 0.0739)	0.0527 (0.019 to 0.0865)	–0.0166 (–0.0652 to 0.0319)	Dominated (–£676)	13.26%	42.70%	25.10%	24.86%	24.42%	24.72%	45.84%
Subgroup analyses														
Older children ≥ 6.5 years (placebo $n = 38$; active treatment $n = 37$; 1000 bootstrap replicates for each of five data sets)	£260 (£114 to £405)	£412 (£222 to £601)	–£152 (–£382 to £79)	0.0430 (–0.0036 to 0.0896)	0.0659 (–0.0016 to 0.1335)	–0.0229 (–0.1022 to 0.0563)	£6611 (SW)	25.82%	7.22%	35.06%	32.96%	31.16%	28.22%	90.38%

continued

TABLE 32 *CUA results for base-case analysis, sensitivity analyses and subgroup analyses (continued)*

	Total costs (95% CI)			QALYs gained relative to baseline utility (95% CI)				Probability that active treatment is		Probability active treatment cost-effective at ceiling ratio			Probability that active treatment is	
Subgroup/ sensitivity analysis	**Active**	**Placebo**	**Difference**	**Active**	**Placebo**	**Difference**	**Cost/QALY**	**Dominant**	**Dominated**	**£20,000**	**£30,000**	**£50,000**	**More effective**	**Less costly**
Younger children < 6.5 years (placebo *n* = 74; active treatment *n* = 68; 1000 bootstrap replicates for each of five data sets)	£559 (£313 to £805)	£458 (£301 to £615)	£101 (–£185 to £387)	0.0324 (–0.0175 to 0.0822)	0.0459 (0.0103 to 0.0816)	–0.0136 (–0.0671 to 0.04)	Dominated (–£7422)	9.34%	54.36%	25.50%	26.64%	27.76%	30.02%	24.96%
Boys (placebo *n* = 63; active treatment *n* = 52; 1000 bootstrap replicates for each of five data sets)	£527 (£267 to £786)	£465 (£299 to £630)	£62 (–£241 to £365)	0.0449 (–0.0081 to 0.0978)	0.0617 (0.0009 to 0.1225)	–0.0168 (–0.0891 to 0.0555)	Dominated (–£3686)	11.96%	47.34%	27.62%	28.48%	29.10%	30.10%	34.52%
Girls (placebo *n* = 49; active treatment *n* = 53; 1000 bootstrap replicates for each of five data sets)	£382 (£169 to £595)	£414 (£232 to £595)	–£32 (–£311 to £247)	0.0275 (–0.0453 to 0.1004)	0.0412 (–0.0207 to 0.1031)	–0.0137 (–0.0808 to 0.0534)	£2322 (SW)	22.08%	29.18%	35.46%	34.32%	33.58%	32.26%	60.64%
Atopy (placebo *n* = 33; active treatment *n* = 35; 1000 bootstrap replicates for each of five data sets)	£449 (£163 to £735)	£398 (£229 to £567)	£51 (–£259 to £361)	0.0381 (–0.019 to 0.0952)	0.0533 (–0.0032 to 0.1098)	–0.0152 (–0.1003 to 0.0699)	Dominated (–£3341)	15.90%	41.34%	34.02%	34.20%	34.54%	35.18%	39.38%
No atopy (placebo *n* = 79; active treatment *n* = 70; 1000 bootstrap replicates for each of five data sets)	£456 (£248 to £664)	£461 (£305 to £616)	–£5 (–£265 to £255)	0.0351 (–0.009 to 0.0793)	0.0525 (0.012 to 0.093)	–0.0174 (–0.069 to 0.0342)	£286 (SW)	12.94%	37.42%	24.82%	24.20%	24.50%	24.32%	51.20%
Severe[b] (placebo *n* = 23; active treatment *n* = 23; 1000 bootstrap replicates for each of five data sets)	£586 (£248 to £924)	£442 (£220 to £664)	£145 (–£260 to £549)	0.0201 (–0.0768 to 0.1169)	0.0739 (0.0065 to 0.1413)	–0.0538 (–0.1818 to 0.0741)	Dominated (–£2690)	5.38%	64.00%	14.46%	15.32%	15.60%	16.76%	24.62%

DOI: 10.3310/hta13370

Subgroup/ sensitivity analysis	Total costs (95% CI)			QALYs gained relative to baseline utility (95% CI)				Probability that active treatment is		Probability active treatment cost-effective at ceiling ratio			Probability that active treatment is	
	Active	Placebo	Difference	Active	Placebo	Difference	Cost/QALY	Dominant	Dominated	£20,000	£30,000	£50,000	More effective	Less costly
Non-severe (placebo $n = 75$; active treatment $n = 65$; 1000 bootstrap replicates for each of five data sets)	£367 (£167 to £566)	£460 (£300 to £619)	–£93 (–£345 to £159)	0.0374 (–0.0023 to 0.0771)	0.0506 (0.0052 to 0.0959)	–0.0131 (–0.0647 to 0.0384)	£7074 (SW)	24.70%	17.90%	37.62%	35.38%	33.28%	30.34%	76.46%
Season 1: enrolled January–March (placebo $n = 44$; active treatment $n = 42$; 1000 bootstrap replicates for each of five data sets)	£451 (£207 to £694)	£326 (£203 to £448)	£125 (–£150 to £400)	0.0434 (0.0027 to 0.084)	0.0534 (0.0051 to 0.1017)	–0.01 (–0.0725 to 0.0525)	Dominated (–£12,451)	7.70%	52.64%	31.04%	33.22%	35.18%	37.90%	17.16%
Season 2: enrolled April–December (placebo $n = 68$; active treatment $n = 63$; 1000 bootstrap replicates for each of five data sets)	£456 (£232 to £679)	£518 (£334 to £702)	–£62 (–£354 to £229)	0.0313 (–0.0271 to 0.0897)	0.0523 (0.0084 to 0.0962)	–0.021 (–0.0888 to 0.0468)	£2963 (SW)	18.20%	25.08%	30.30%	29.08%	28.08%	25.86%	67.26%
Early trial period with AM (placebo $n = 37$; active treatment $n = 35$; 1000 bootstrap replicates for each of five data sets)	£417 (£133 to £701)	£566 (£331 to £802)	–£149 (–£523 to £224)	0.0213 (–0.0835 to 0.126)	0.0334 (–0.0315 to 0.0984)	–0.0122 (–0.1136 to 0.0893)	£12,249 (SW)	30.68%	13.92%	44.48%	42.54%	40.84%	38.00%	78.76%
Later trial period without AM (placebo $n = 75$; active treatment $n = 70$; 1000 bootstrap replicates for each of five data sets)	£472 (£266 to £677)	£381 (£249 to £513)	£91 (–£154 to £335)	0.0435 (0.0142 to 0.0729)	0.0622 (0.0241 to 0.1004)	–0.0187 (–0.0655 to 0.028)	Dominated (–£4838)	5.96%	60.66%	17.36%	18.54%	19.58%	21.10%	24.20%

SW, southwest quadrant of the cost-effectiveness plane. ICERs in this quadrant indicate that active treatment is less costly and less effective than placebo and ICERs *higher* than the ceiling ratio should be considered cost-effective, as they indicate that substantial savings could be accrued at the loss of relatively few QALYs.

a Represents absolute QALYs accrued over the 9-month trial period, rather than QALYs gained relative to baseline.

b Severe disease was defined as a clinical severity score above 0.62 (the upper quartile limit of the sample). Clinical severity was defined as the first principal component of the baseline variables – frequency of surgery attendance in last 12 months for ear problems; tympanogram readings; age at first episode of hearing infection/problem; total reported episodes of ear problems over last 12 months; RESP score – identified in an analysis of these variables ignoring randomisation group.

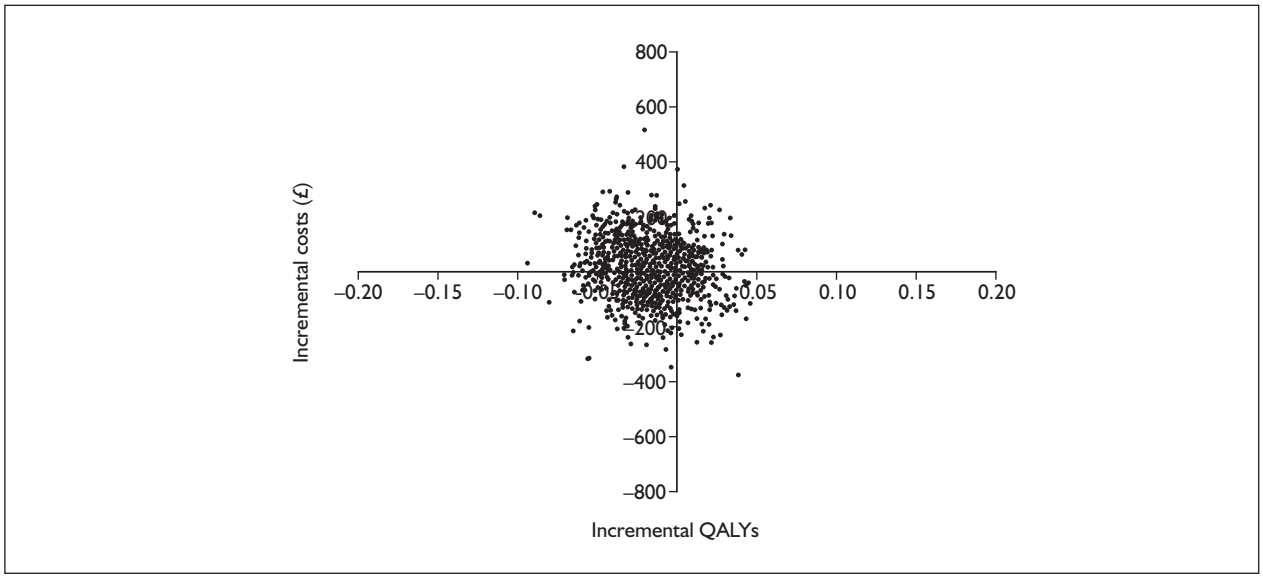

FIGURE 21a *Base-case analysis: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo on the cost-effectiveness plane. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

analysis: children for whom the HUI3 and/or OM8-30 questionnaires were not completed tended to have higher costs if they received placebo and lower costs if they received active treatment than children for whom utility data were available.

In addition to having higher average costs, the active treatment group accrued fewer QALYs per child than the placebo group, regardless of whether the domain or facet model was used to estimate utilities, although this difference did not reach statistical significance. Regardless of which mapping model was used to estimate missing utility data, active treatment was dominated by placebo, and the probability of treatment being cost-effective at a £20,000 per QALY threshold was just 39% (*Figure 24c–d*).

Basing costs on the report forms that parents (or guardians) completed at 3 and 9 months, rather than using the resource use data extracted from medical records, substantially increased the probability that use of intranasal steroids would increase NHS costs from 54% to 95% (*Figure 25*) and increased the incremental cost of treatment from £11 to £185, although the difference did not

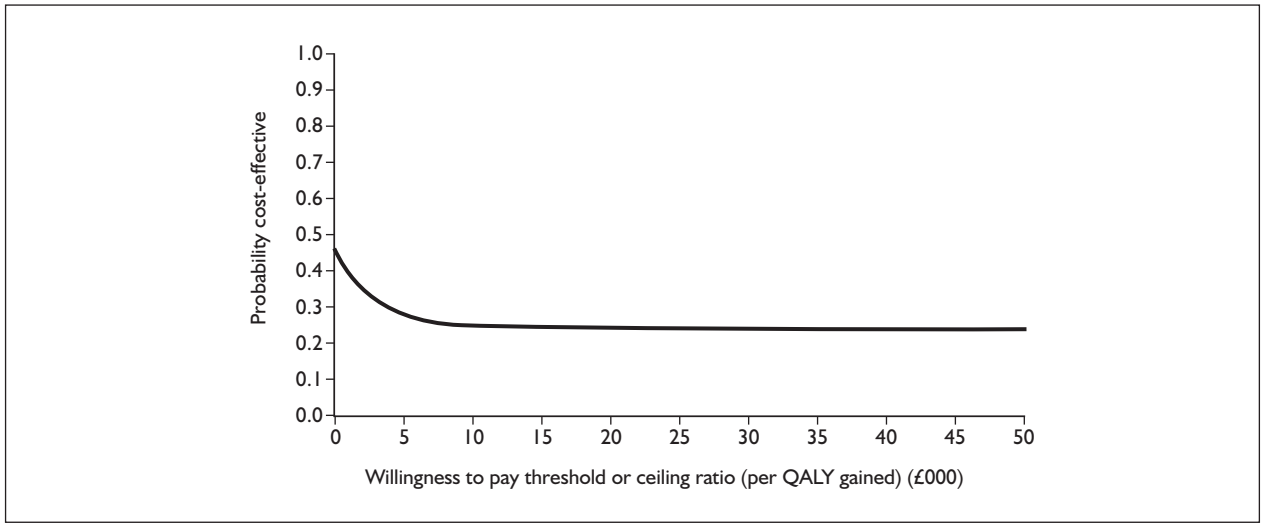

FIGURE 21b *Base-case analysis: CEAC showing the probability that intranasal steroids are cost-effective at a range of ceiling ratios representing possible values for the maximum amount that society may be willing to pay to gain an additional QALY.*

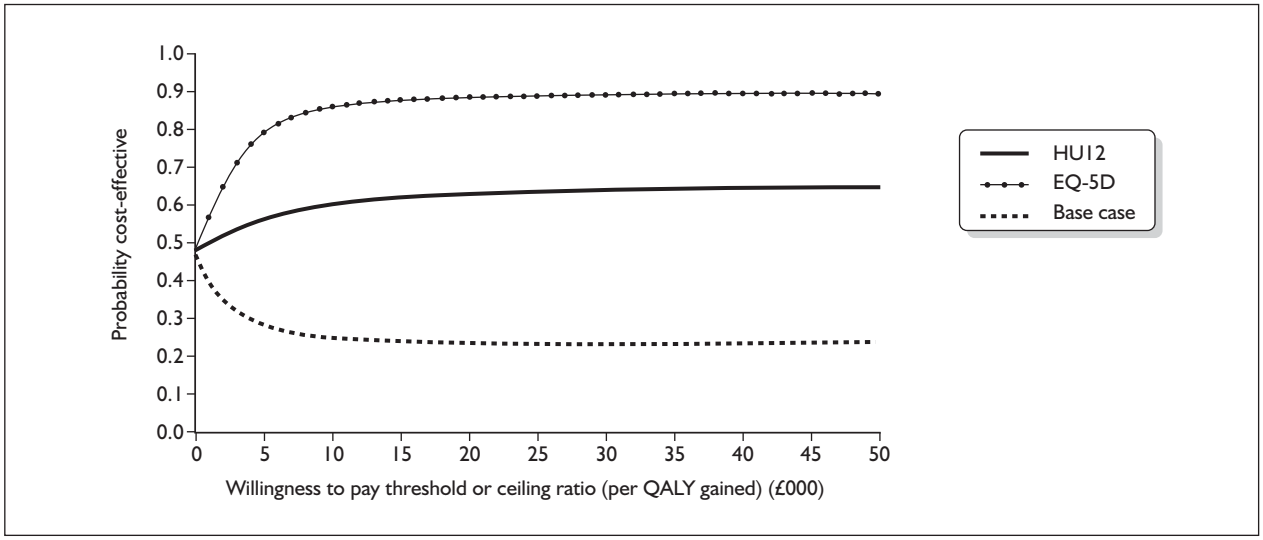

FIGURE 22a *CEACs for analyses using HUI2 and EQ-5D: utilities were based on either the HUI2 or EQ-5D$_5$ instruments and include values imputed in the main multiple imputation analysis (in which predicted HUI3 utilities from the mapping models were included as explanatory variables, but predictions of HUI2 and EQ-5D utilities were not). Other than the instruments used to generate utilities, the data, assumptions and methods used in this analysis were the same as for the base-case analysis.*

reach statistical significance on a two-tailed test. When resource use estimated by parents was used in the analysis, the probability of steroids being cost-effective relative to placebo at a £20,000 per QALY threshold fell to 14%.

By contrast, adding in the cost of one baseline tympanometric assessment for all children in both arms had no impact on incremental costs or benefits, as costs increased by the same amount for all children (data not shown).

Subgroup analyses

The CUA was repeated for the six sets of subgroups that were investigated in the CEA, using the same

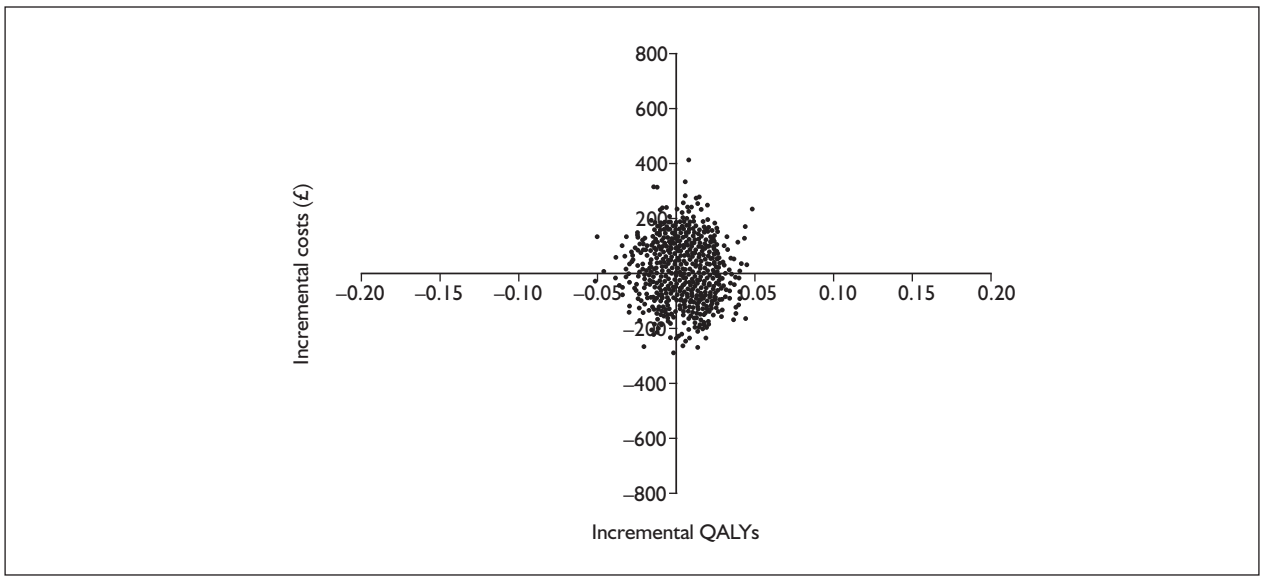

FIGURE 22b *HUI2: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. Utilities were based on the HUI2 instrument and include values imputed in the main multiple imputation analysis (in which predicted HUI3 utilities from the facet mapping model were included as explanatory variables, but predictions of HUI2 and EQ-5D utilities were not). All other parameters were conducted using the same data and methods as the base-case analysis. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

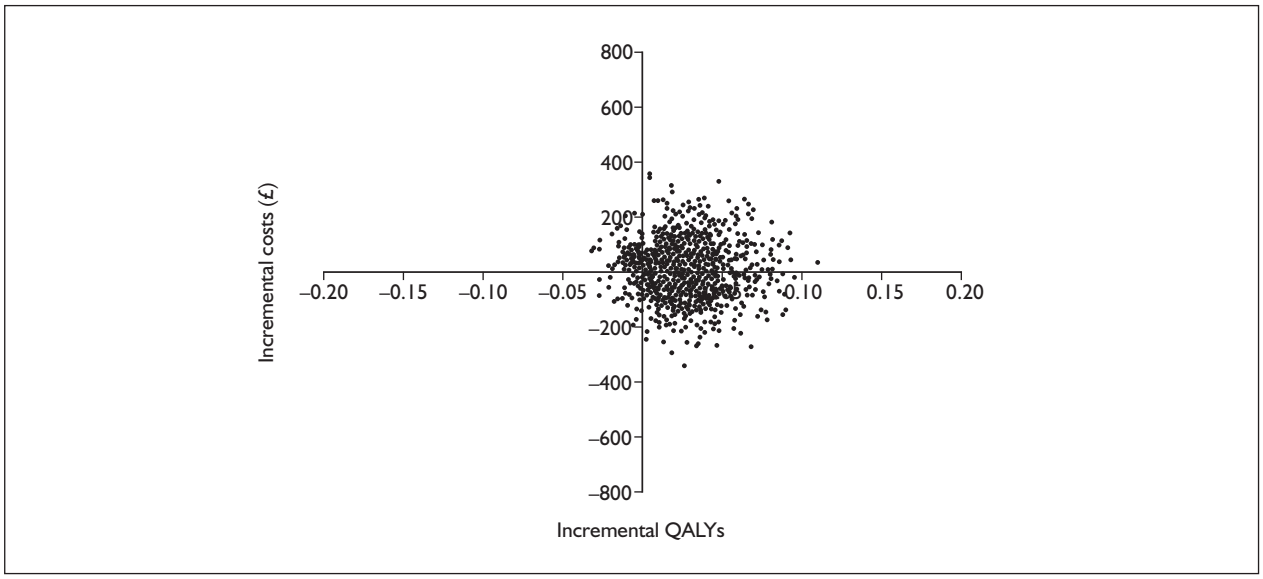

FIGURE 22c *EQ-5D$_5$: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. Utilities were based on the EQ-5D instrument and include values imputed in the main multiple imputation analysis (in which predicted HUI3 utilities from the mapping models were included as explanatory variables, but predictions of HUI2 and EQ-5D utilities were not). All other parameters were conducted using the same data and methods as the base-case analysis. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

assumptions and methods used for the base-case analysis.

As for the CEA, subgrouping children by age had a dramatic effect on the results, although the trends observed differ based on how outcomes are measured. Within the subgroup of children aged over 6.5 years, the group receiving intranasal steroids accrued lower costs than the group assigned to placebo (*Figure 26b*), while active treatment was found to be more costly within the subgroup of younger children (*Figure 26c*). However, for both subgroups, the active treatment arm accrued fewer QALYs than the placebo arm, although the difference between the groups was larger in older children. This contrasts with the

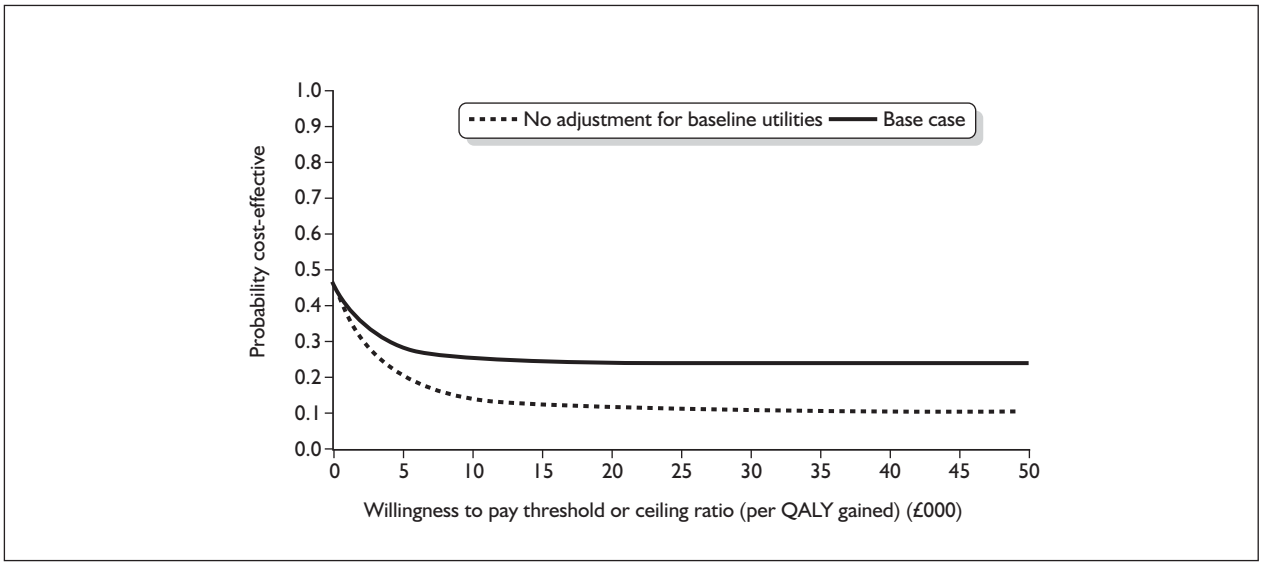

FIGURE 23a *CEAC for analysis with no adjustment for baseline utility. All other parameters were conducted using the same data and methods as the base-case analysis.*

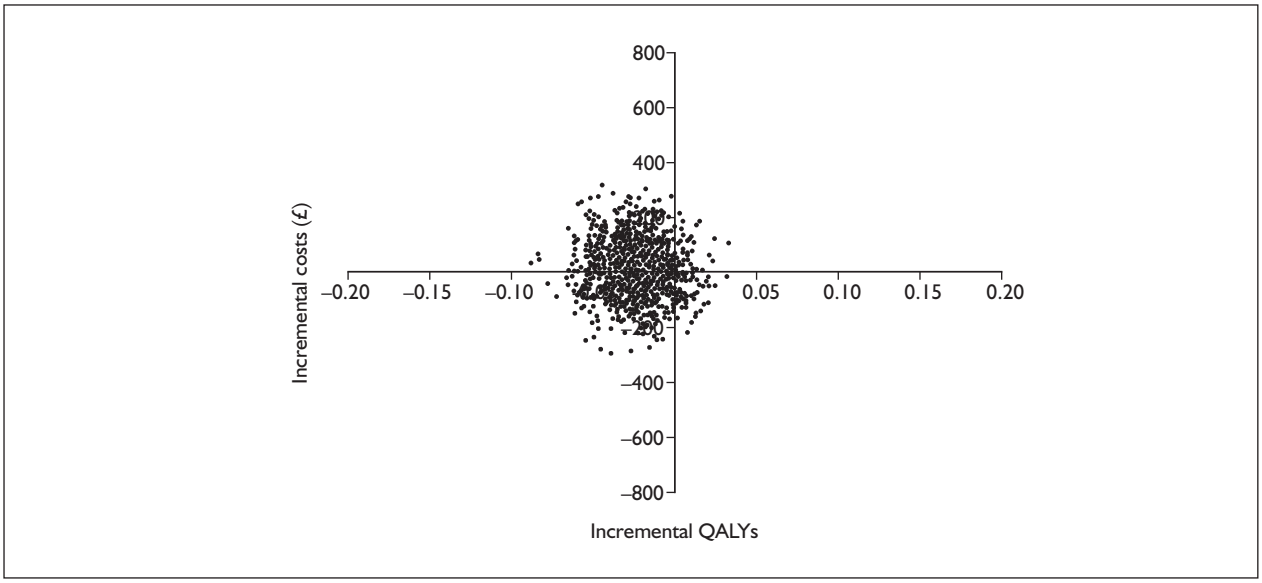

FIGURE 23b *No adjustment for baseline utility: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. The total number of QALYs calculated for each child (including imputed values) was used directly in bootstrapping analyses, with no adjustment for baseline utility; all other parameters were conducted using the same data and methods as the base-case analysis. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

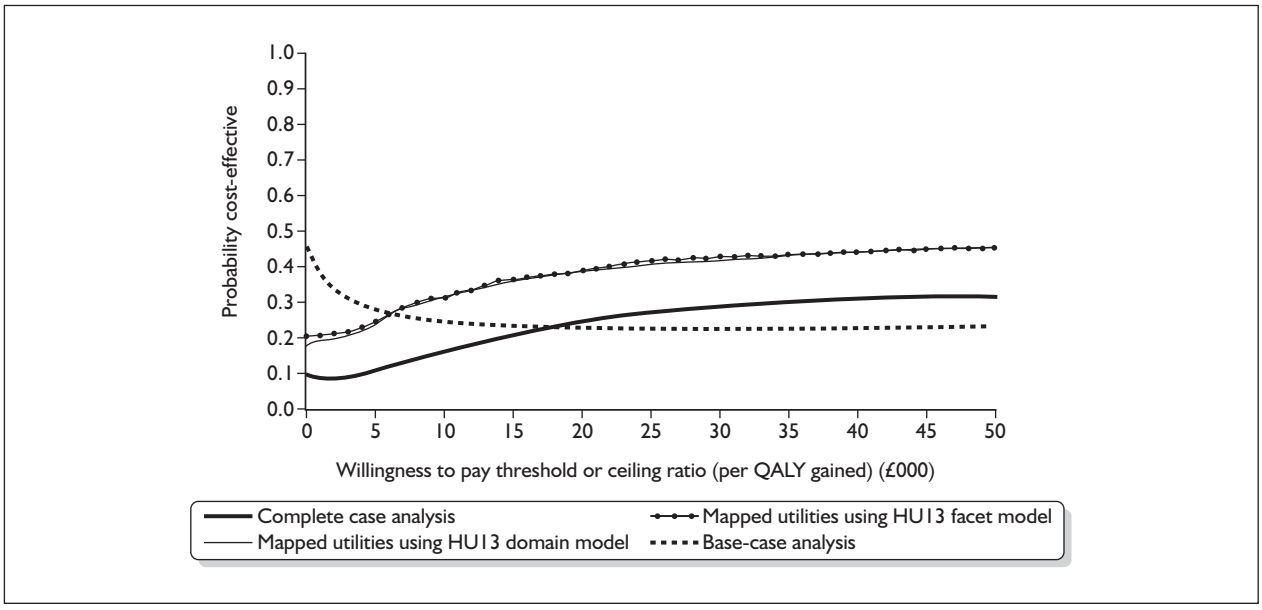

FIGURE 24a *Complete case analysis and analyses including mapped utilities: CEAC. Within the complete case analysis, only children who fully completed the HUI3 questionnaire at baseline and at both the 3- and 9-month follow-ups and had full resource use data were included and no values were imputed. Within the analyses using mapped utilities, missing utility data were imputed (where possible) using two of the mapping algorithms described in Appendix 15 that estimate HUI3 utilities based on OM8-30 scores: the OLS model using OM8-30 facet scores and the OLS model using OM8-30 domain scores (plus age and sex). Multiple imputation analysis was not used for the complete case analysis or for either of the analyses using mapped utilities; these analyses were therefore based on 1000 bootstrap replicates with a single set of raw data.*

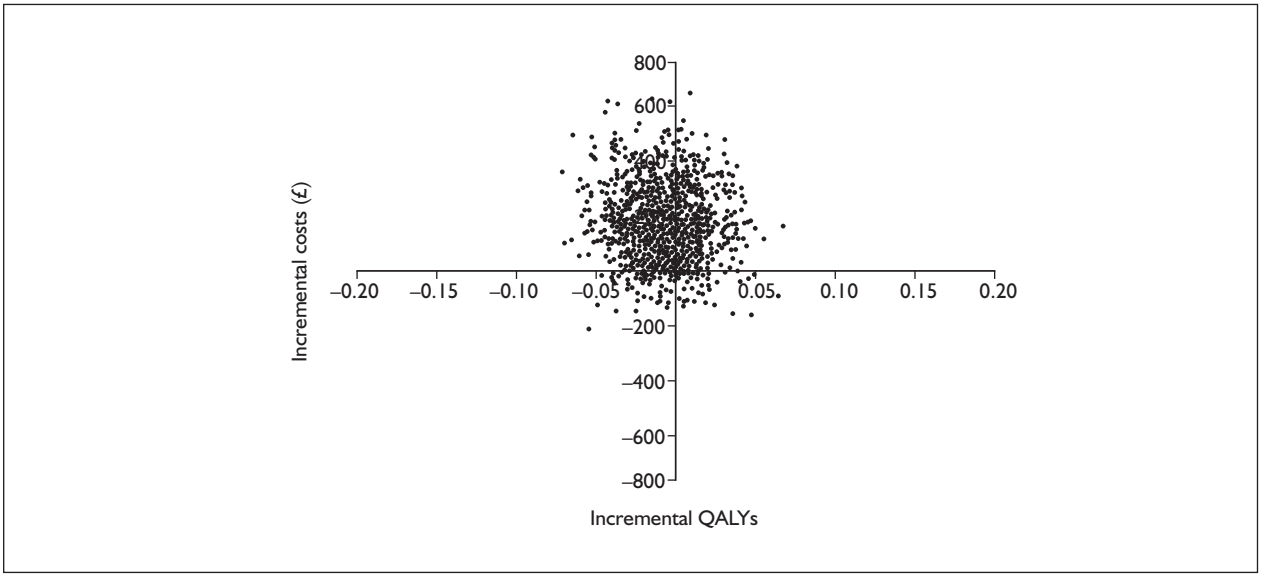

FIGURE 24b *Complete case analysis: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo, including only children who fully completed the HUI3 questionnaire at baseline and at both the 3- and 9-month follow-ups; all other parameters were conducted using the same data and methods as the base-case analysis.*

finding in the CEA, in which treatment appeared to slightly increase the probability of cure in older children but reduce it in younger children. The difference between these analyses appears to result (at least in part) from differences in the time horizon used for outcomes: older children randomised to active treatment tended to have a higher chance of tympanometric cure at 1 and 3 months than the placebo group, but had a slightly lower chance of being cured at 9 months; by contrast, younger children randomised to active treatment had a lower probability of being cured than those in the placebo group at all three time points. However, these variable findings are probably due to chance as there is no simple explanation.

Given that both the incremental costs and incremental QALYs are negative in older children, the point estimate for this ICER falls in the

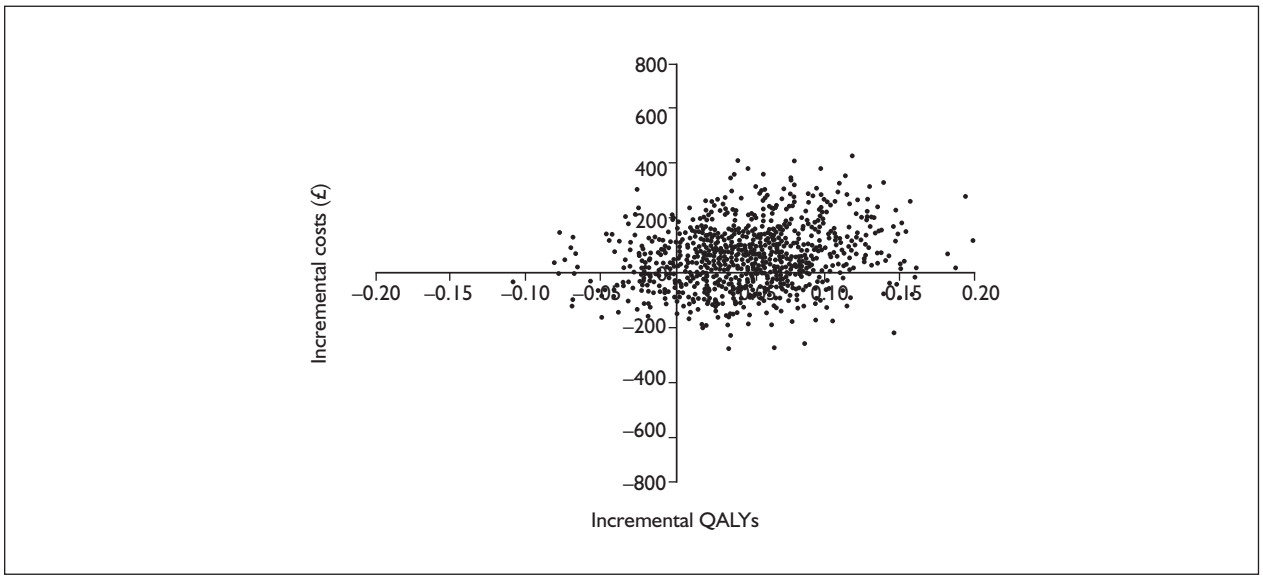

FIGURE 24c *Mapped utilities using the OM8-30 facet model: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. Missing utility data were imputed (where possible) using the OLS mapping model using OM8-30 facet scores (Appendix 15), with no multiple imputation of either costs or benefits.*

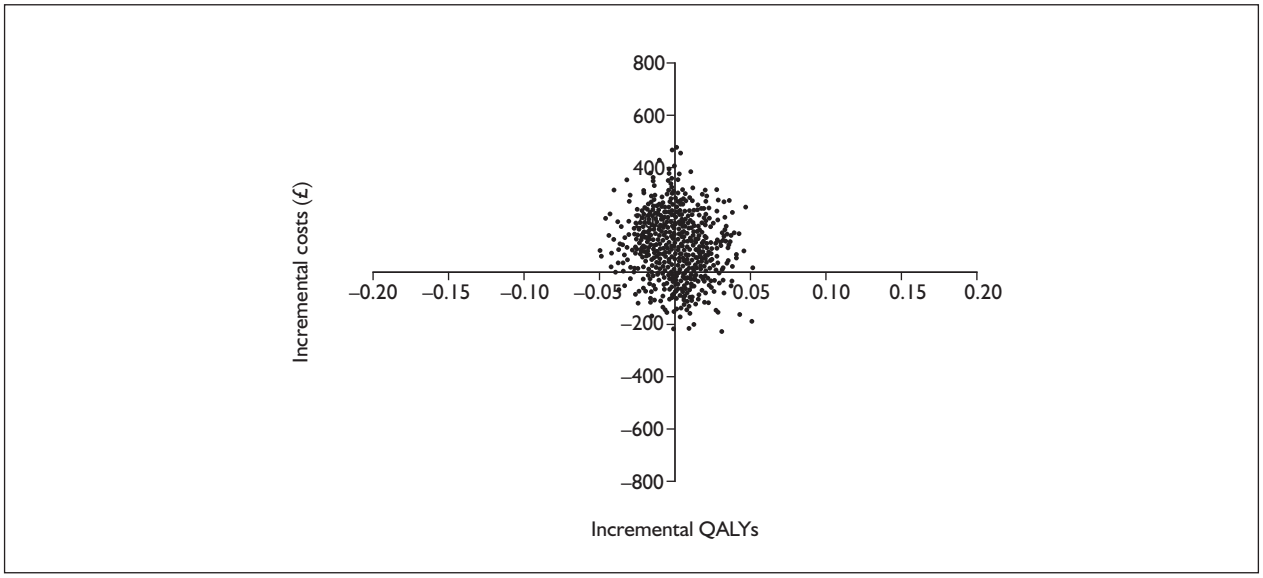

FIGURE 24d *Mapped utilities using the OM8-30 domain model: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. Missing utility data were imputed (where possible) using the OLS mapping model using OM8-30 domain scores plus age and sex (Appendix 15), with no multiple imputation of either costs or benefits.*

south-west quadrant and suggests that using active treatment would save £6611 per QALY lost compared with placebo. In the south-west quadrant, ICERs have the opposite interpretation to those in the north-east quadrant, whereby treatment would be considered cost-effective if its ICER were above the ceiling ratio (rather than below); this means that treatment would not be considered cost-effective in older children at an ICER of £6611 per QALY lost. By contrast, treatment is dominated by placebo for younger children and for the study population as a whole.

Despite the substantial difference in incremental costs and ICERs, the probability of active treatment being cost-effective at a £20,000 per QALY ceiling ratio was relatively similar across the two groups, being 35% in older children and 26% in younger children (*Figure 26a*).

The difference in incremental costs between the sexes was also pronounced, although less extreme than the finding for age. In girls, use of steroids was associated with slightly lower costs than the placebo group by an average of £32 per child,

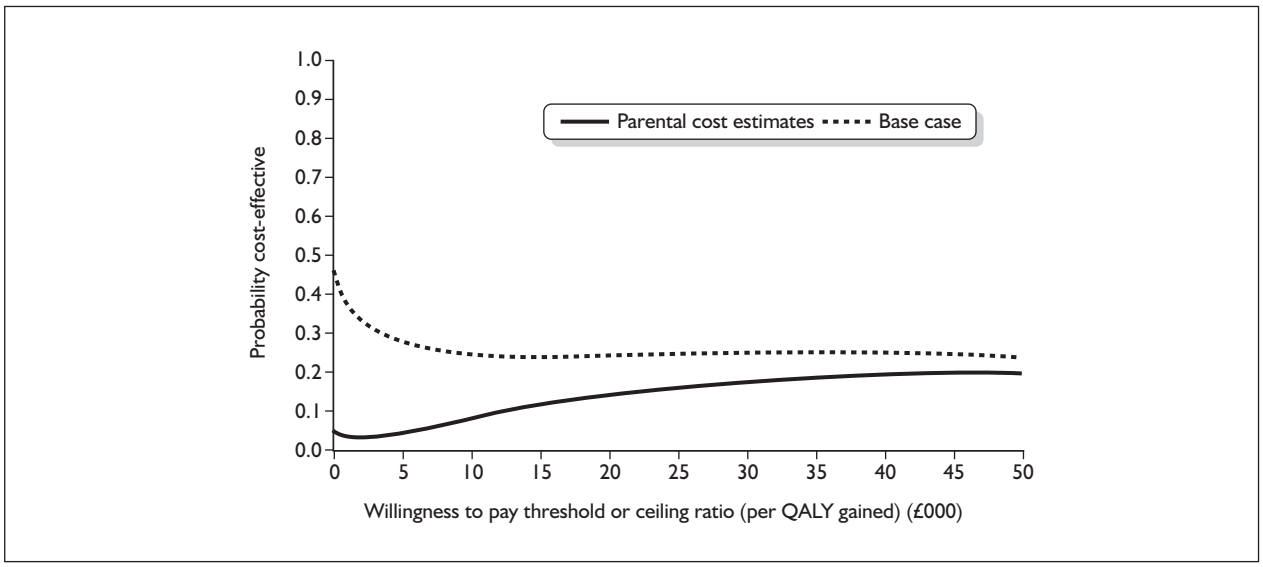

FIGURE 25a *CEAC for analysis using costs derived from parents' (or guardians') resource use questionnaires; all other parameters were conducted using the same data and methods as the base-case analysis.*

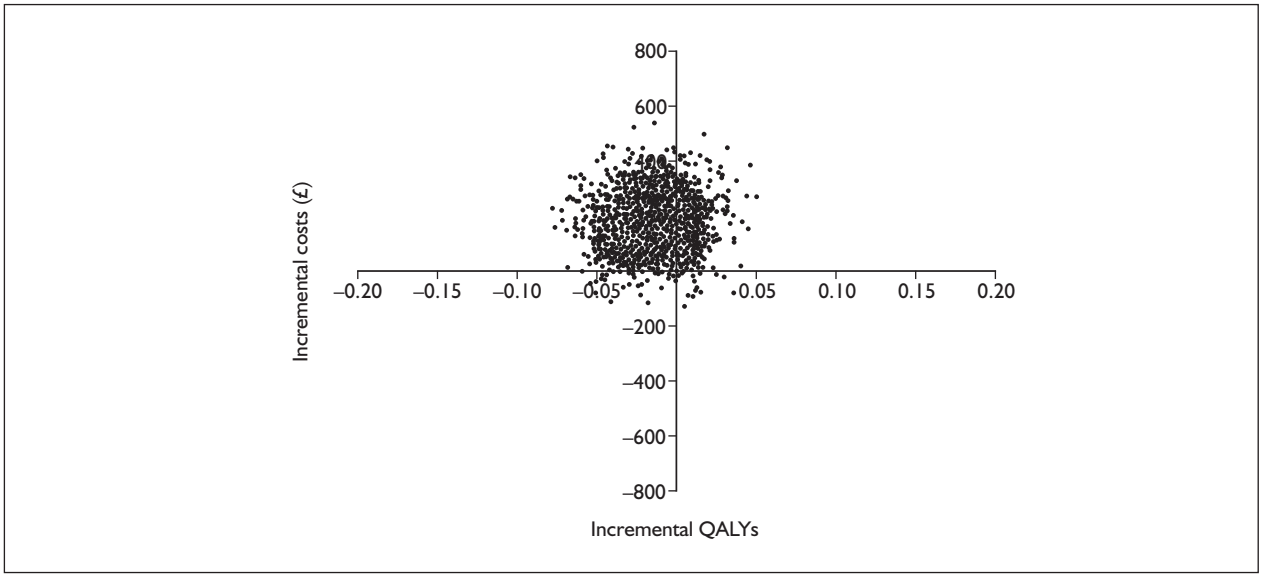

FIGURE 25b *Costs based on parents' (or guardians') resource use questionnaires: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. All other parameters were conducted using the same data and methods as the base-case analysis. For clarity, only the results of the first 200 bootstrap replicates for each of the five imputed data sets are shown; all values are per child.*

whereas in boys, active treatment increased costs by an average of £62 per child, although neither difference reached statistical significance (see *Table 32*). Although boys had greater improvements in QoL relative to baseline than girls, the active treatment group accrued 0.014–0.017 fewer QALYs than the placebo group regardless of sex. Based on the point estimates for ICERs, active treatment was dominated by placebo for boys (with a 28% probability of being cost-effective at a £20,000 per QALY threshold) and saved £2322 per QALY lost for girls (with a 35% probability of being cost-effective at this threshold; *Figure 27*).

Subgrouping by the presence/absence of atopy had little impact on QoL or the probability of treatment being cost-effective within the CUA, although active treatment was associated with higher costs (£51 per child) than placebo in children with atopy, compared with cost savings of £5 per child relative to placebo in the group with no atopy at baseline (*Figure 28* and *Table 32*).

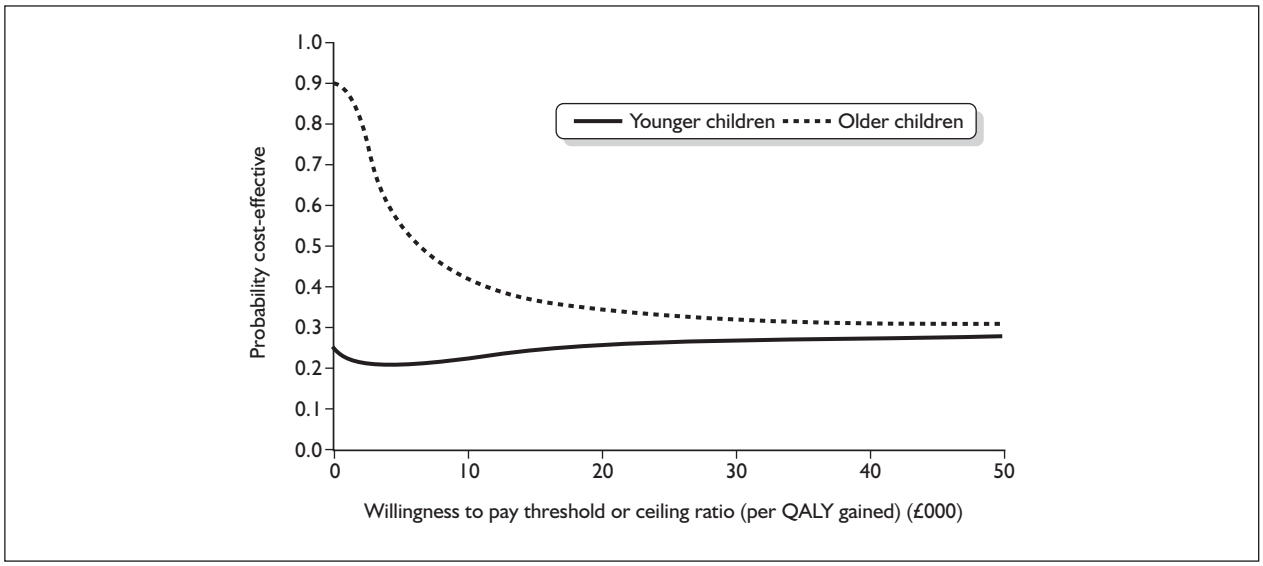

FIGURE 26a *CEACs for subgroups stratified by age. Both analyses were conducted using the same methods as the base-case analysis.*

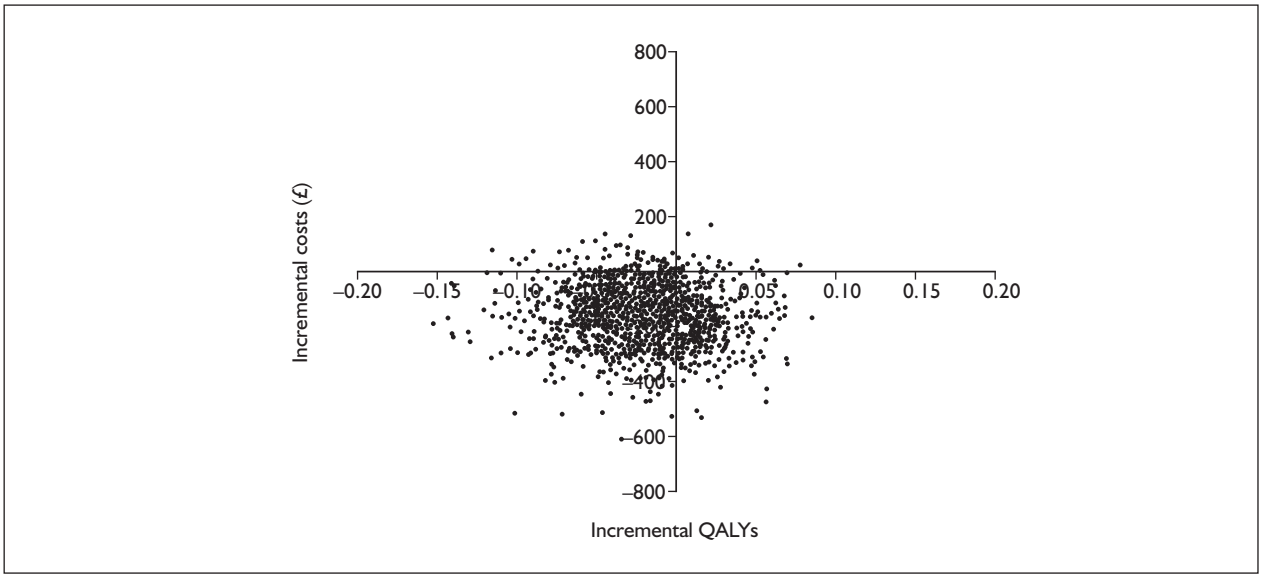

FIGURE 26b *Older children (≥ 6.5 years at baseline): scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo. In this scattergraph and all of those that follow, the results of only the first 200 bootstrap replicates for each of the five imputed data sets are shown and all values are per child.*

Subgrouping by disease severity (severe disease was defined as a clinical severity score above 0.62, the upper quartile limit of the sample) also had a substantial effect on cost-effectiveness (*Figure 29*). In children with severe disease, use of intranasal steroids increased NHS costs by £145 per child compared with placebo (with a 75% probability that treatment is more costly). By contrast, in the less severe subgroup, active treatment was associated with lower costs than placebo (difference: £93 per child). Although the absolute difference in QALYs and the probability of treatment being less effective than placebo were lower in children with non-severe disease, there was relatively little difference in the probability of active treatment being cost-effective at a £20,000–30,000 per QALY threshold (*Figure 29*).

The incremental cost of treatment also varied with season: among children recruited to the study between January and March (inclusive), the active treatment arm tended to accrue higher NHS costs

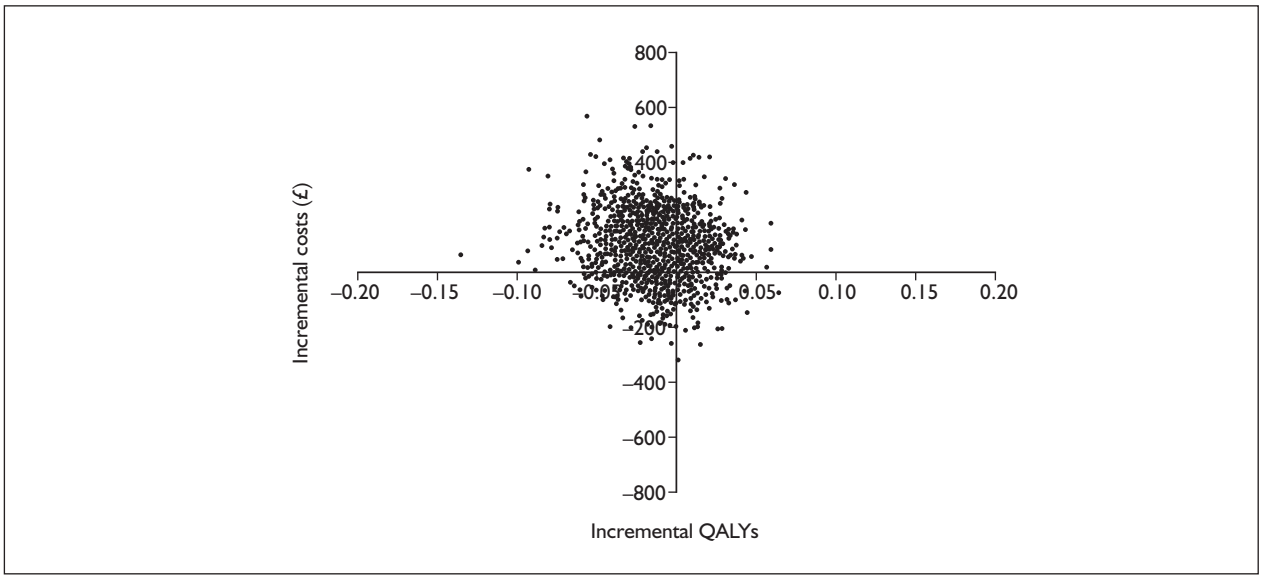

FIGURE 26c *Younger children (< 6.5 years at baseline): scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

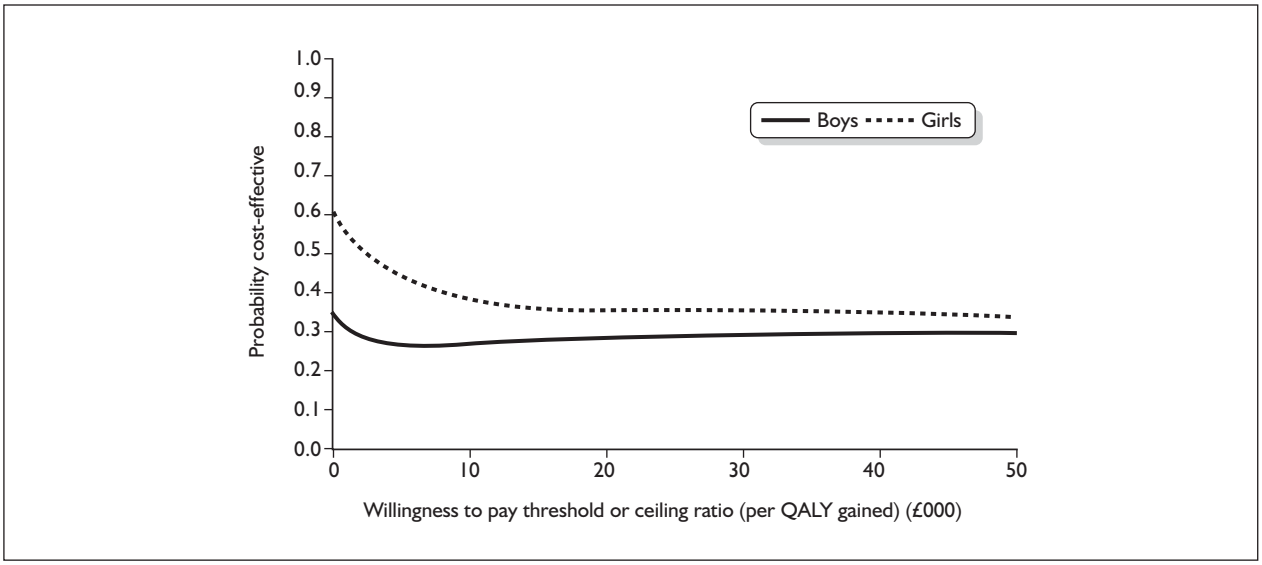

FIGURE 27a *CEACs for subgroups stratified by sex. Both analyses were conducted using the same methods as the base-case analysis.*

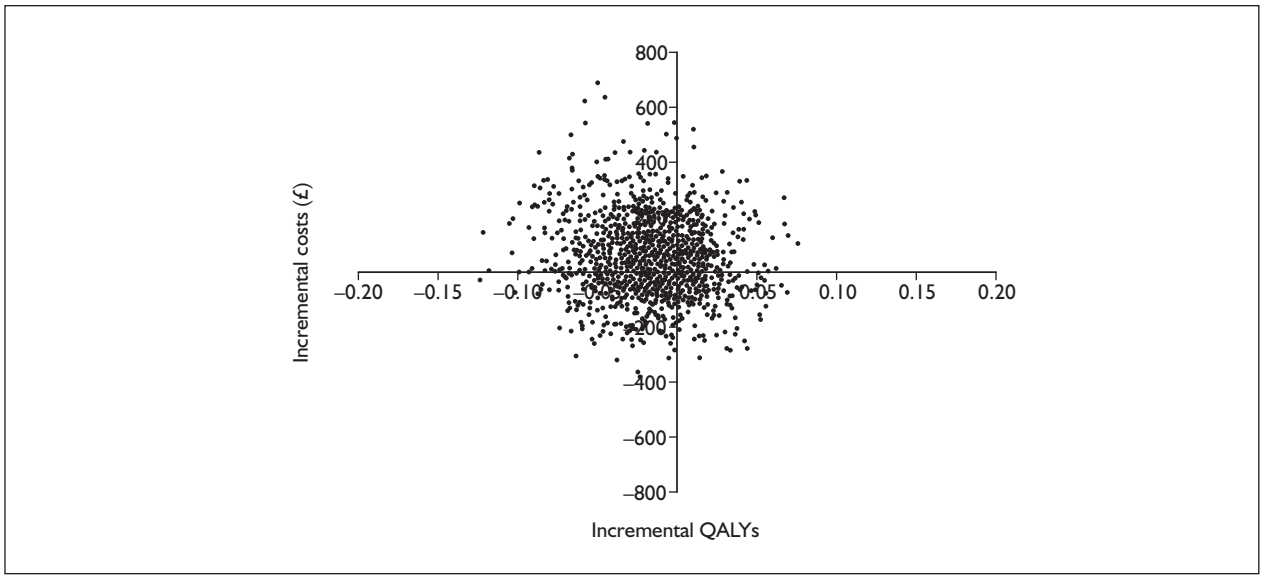

FIGURE 27b *Boys: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

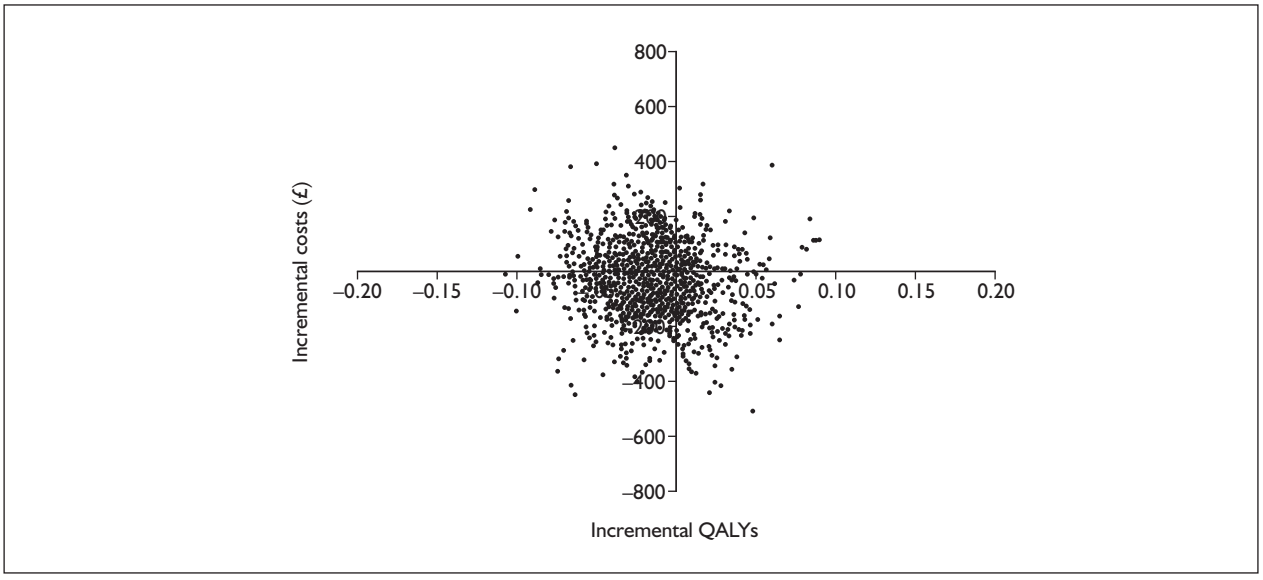

FIGURE 27c *Girls: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

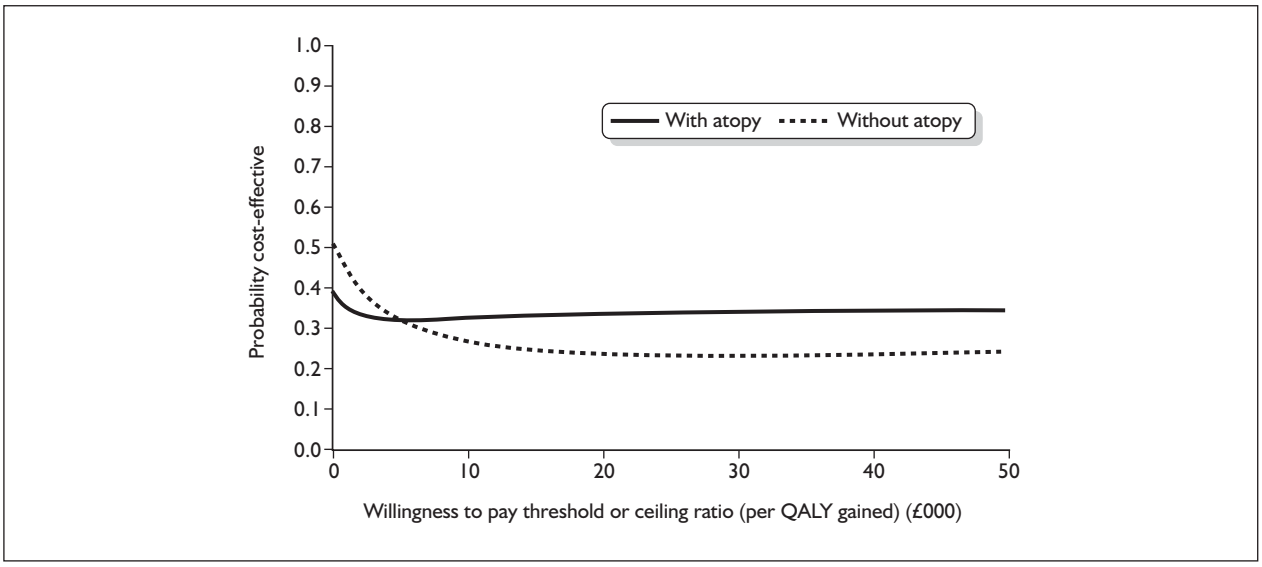

FIGURE 28a *CEACs for subgroups stratified by the presence/absence of atopy. Both analyses were conducted using the same methods as the base-case analysis.*

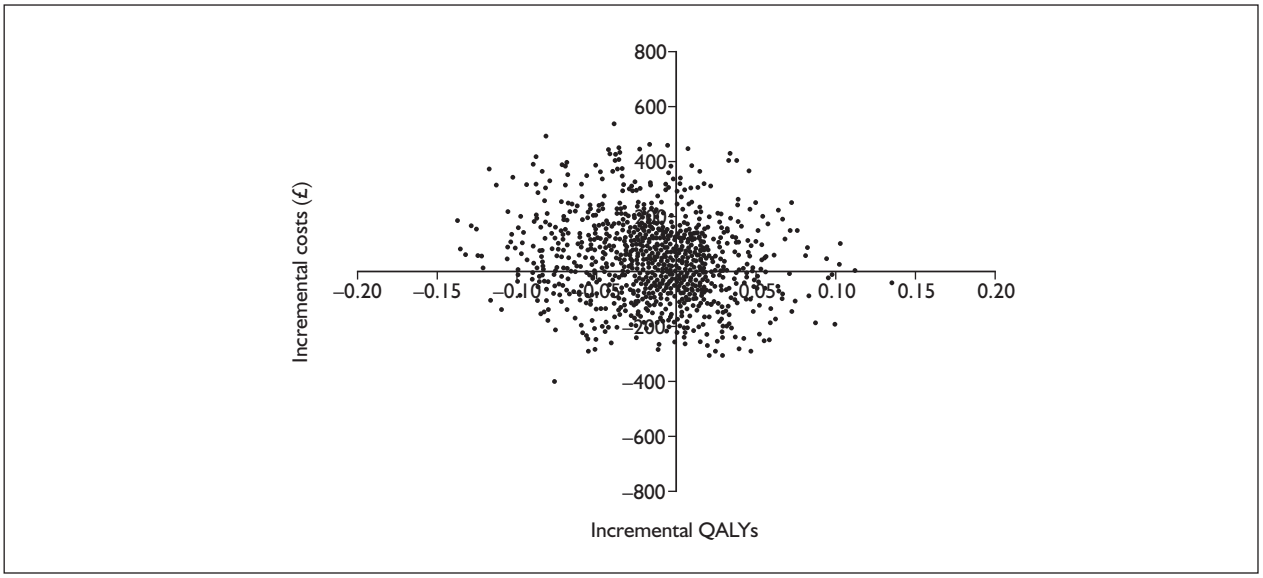

FIGURE 28b *Children with atopy: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

than the placebo group and active treatment was dominated by placebo and had a 31% chance of being cost-effective at a £20,000 per QALY ceiling ratio (*Figure 30*). By contrast, among children recruited between April and December, there was a non-significant trend suggesting that active treatment is less costly than placebo, would save £2963 per QALY lost and would have a 30% probability of being cost-effective.

Given that substantial changes were made to the protocol part-way through the study that resulted in the removal of the AM period, changes to child recruitment, the addition of utility instruments and changes to the collection of resource use data, the costs and benefits of treatment in children recruited before and after the protocol change were evaluated in a subgroup analysis. During the initial trial period (with AM), for which most utility data came from the OM8-30 mapping analysis, costs were lower in the active treatment group than in the placebo group (probability = 79%) and there was a 44% chance that treatment was cost-effective at a £20,000 per QALY threshold (*Figure 31a–c*). Among children recruited after the protocol change, total costs in the active treatment arm were an average of £91 per child higher than those for placebo, and active treatment had a 17% chance of being cost-effective. The difference in costs is unlikely to be due to the changes in the way that resource use data were collected as such amendments simply resulted in the collection of

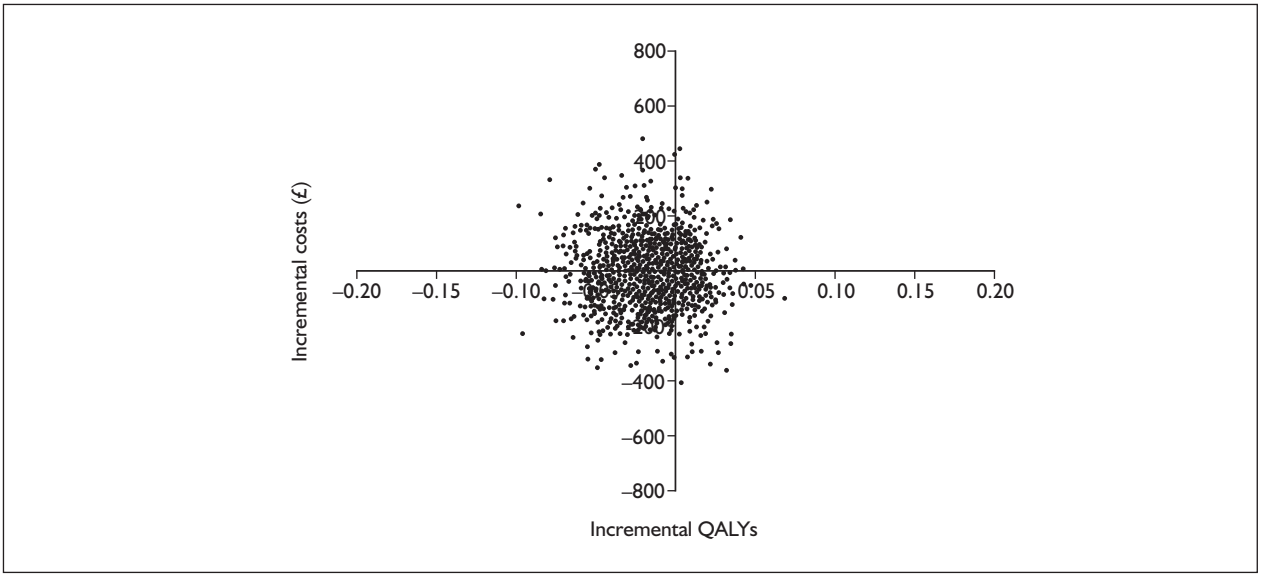

FIGURE 28c *Children without atopy: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

additional data, but this explanation is hard to completely exclude. It is also unlikely to reflect changes in the management of OME over a short study time frame, with no major changes in practice, but earlier study entry (i.e. in the natural history) may have pushed up initial antibiotic and medication costs (non-significantly) in the group that took slightly longer to resolve. However, as the clinical trial showed no efficacy differences (using a sensitivity analysis), these cost differences might reasonably be considered as chance subgroup findings. The difference in the incremental QALY loss from treatment may be (at least in part) due to the much greater degree of missing data in the early trial period, which were imputed using multiple imputation.

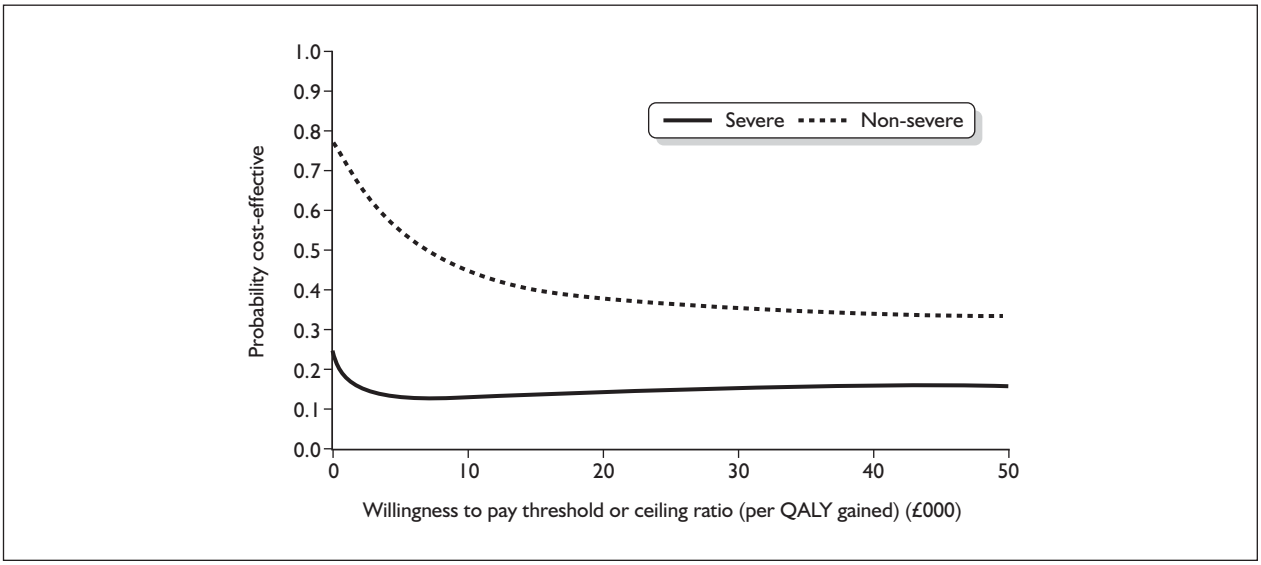

FIGURE 29a *CEACs for subgroups stratified by disease severity [categorised based on clinical severity score (see Chapter 4, Clinical outcomes) using a cut-off of 0.62 (the 75th percentile)]. Both analyses were conducted using the same methods as the base-case analysis.*

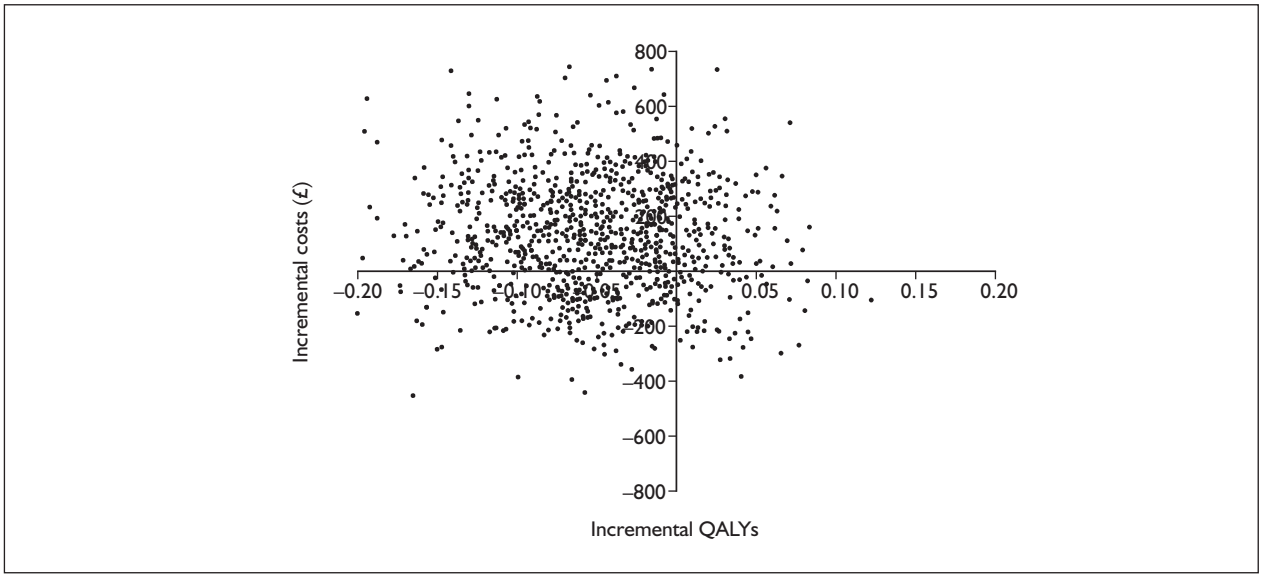

FIGURE 29b *Children with severe disease (highest 25% of children by severity score): scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

Conclusions

The economic evaluation demonstrates that intranasal steroids have no significant effect on either costs or benefits, although there was a non-significant trend towards higher costs in the treatment group than in the placebo group, which is likely to be attributable to the drug acquisition cost.

However, the trend for health outcomes differs depending on how benefits were measured. The CEA base-case analysis observed a slightly, but not significantly, higher chance of a tympanometric cure at the composite end point of 1 or 3 months than for placebo. However, sensitivity analyses evaluating outcomes at individual time points suggested that the treatment group had superior outcomes only at the 3-month point, with placebo

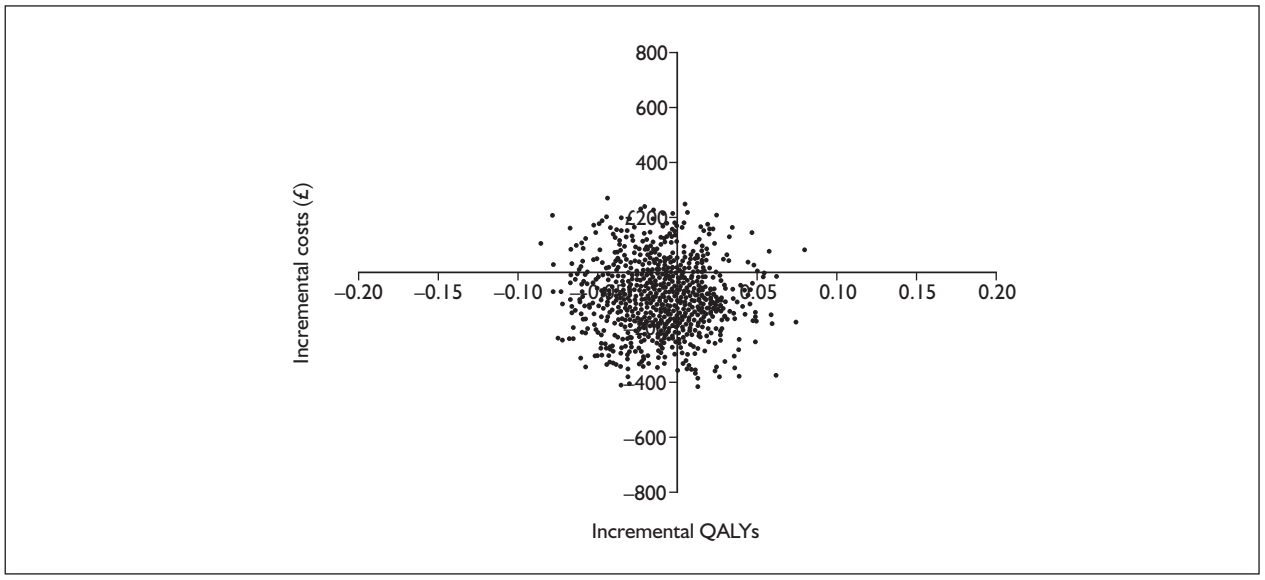

FIGURE 29c *Children with non-severe disease (lowest 75% of children by severity score): scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

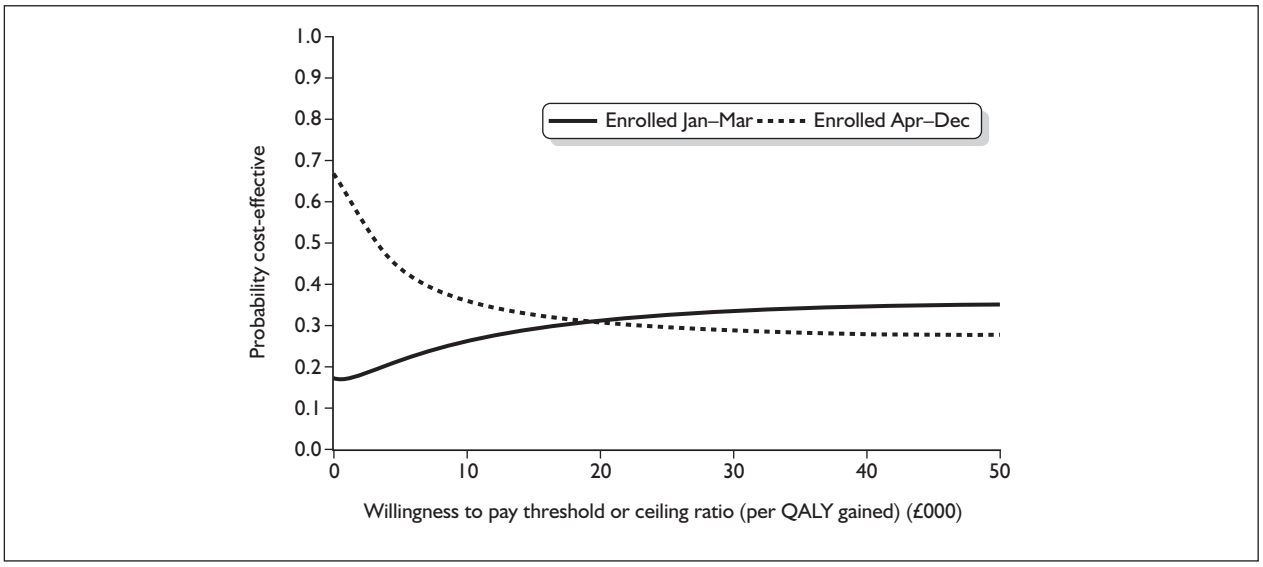

FIGURE 30a *CEACs for subgroups stratified by the season at the time of enrolment. Both analyses were conducted using the same methods as the base-case analysis.*

being non-significantly superior at 1 and 9 months after start of treatment.

By contrast, the CUA found a non-significant trend towards lower numbers of QALYs in the active treatment group than for placebo. Furthermore, although trends were sensitive to the methods used to impute missing data and the utility instrument used, utilities were generally lower for the treatment group than for the placebo group at all time points (see Analysis of utility measures) – including at the 3-month time point when the tympanometric cure occurred more commonly in the treatment group.

The difference between the results of the CEA and those of the CUA may be due to chance, as neither difference reached statistical significance within the total trial population. The possibility of this finding being due to chance is also highlighted by the observation that a small but non-significant gain in QALYs was observed with treatment when QALYs were based on two other utility measures (HUI2 and EQ-5D$_5$). Furthermore, the sign of

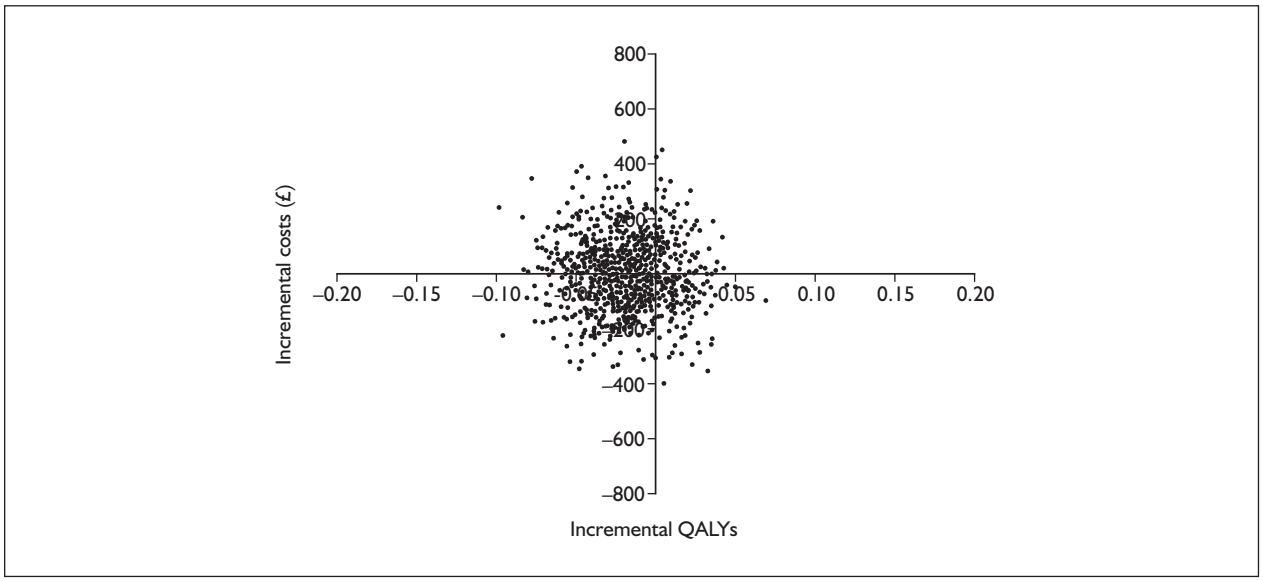

FIGURE 30b *Children randomised in January, February or March: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

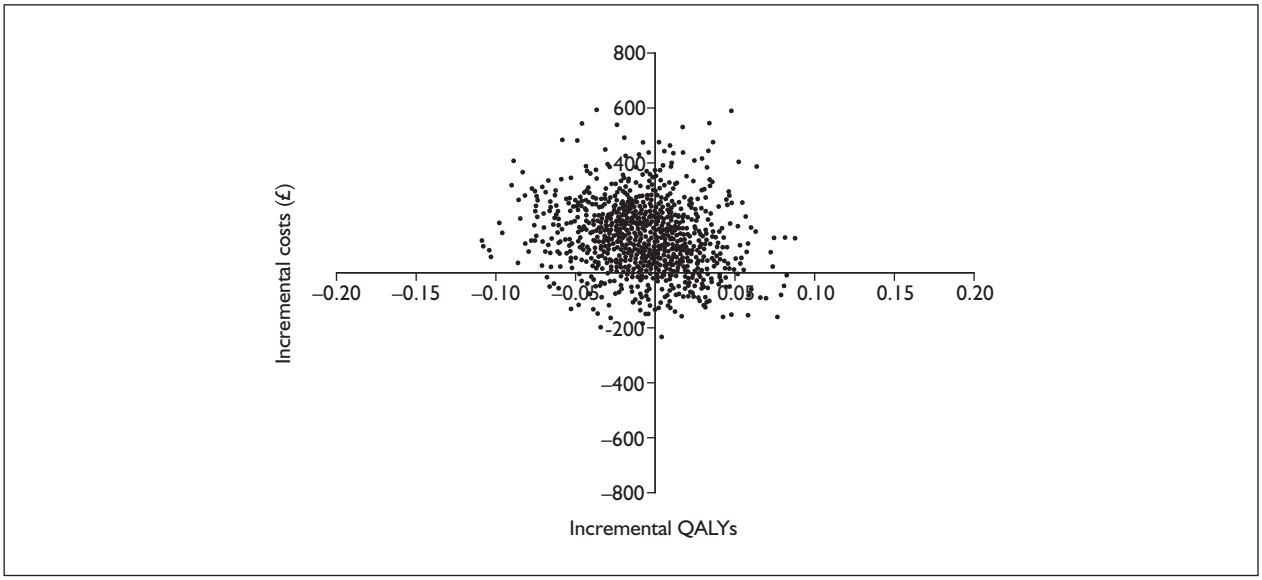

FIGURE 30c *Children randomised between April and December: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

the difference was also sensitive to small changes in other assumptions, while the difference in tympanometric cure rates was very sensitive to the timing of the measurement and differed between subgroups. The finding may also result from the difference in the time horizons used for outcomes in the two analyses (3 months for the CEA and 9 months for the CUA); on this basis, the CUA may better reflect the likely cost-effectiveness of treatment. However, this finding deserves further investigation to rule out the possibility that steroid treatment causes side effects that reduce children's health-related QoL and outweigh the benefits of treatment: particularly in patients with severe disease, in whom the QALY loss was greatest [0.0538 (95% CI –0.0741 to 0.1818) QALYs lost per patient compared with placebo] and where a non-significant reduction in the probability of cure was also observed in the CEA. Although analyses conducted to date have identified no significant increase in side effects or viral infections or any significant association between side effects/infections and health-related QoL, it is possible that the difference is due to a side effect not fully captured by the reported measures.

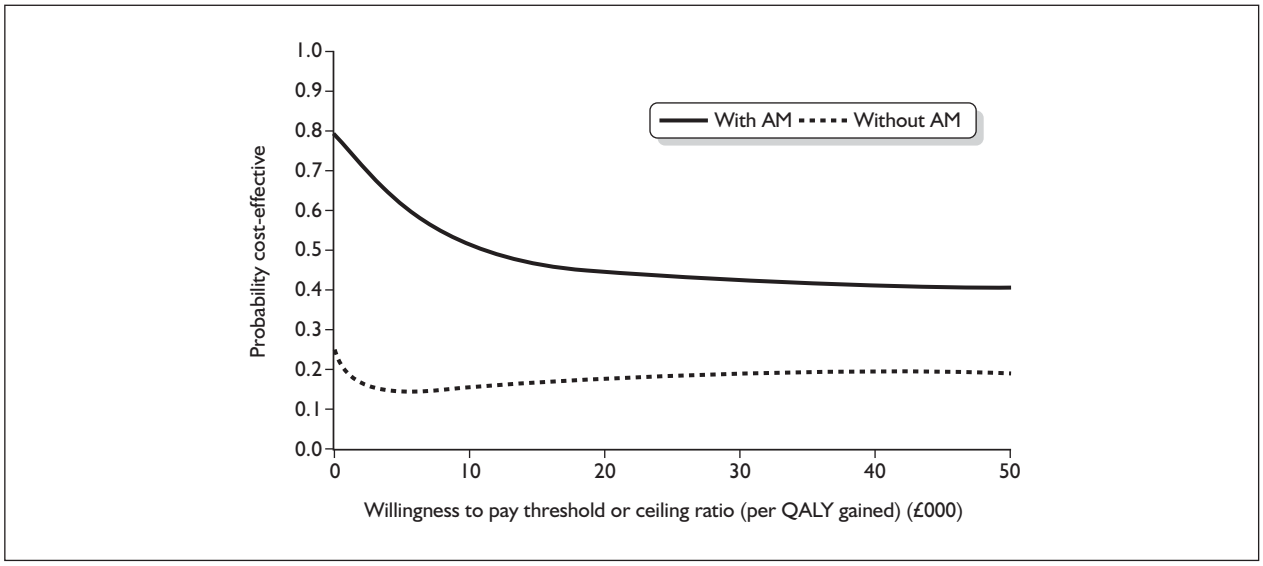

FIGURE 31a *CEACs for subgroups stratified into before and after the protocol amendment that led to the introduction of utility measures and the removal of AM. Both analyses were conducted using the same methods as the base-case analysis.*

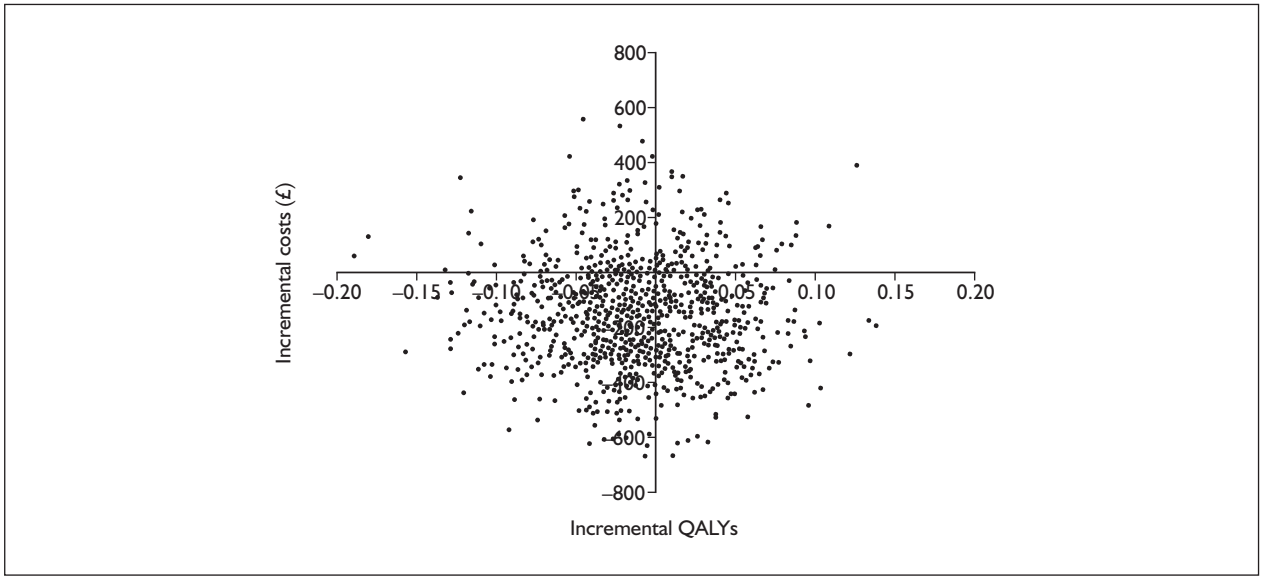

FIGURE 31b *Initial trial period with AM: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

Overall, the economic evaluation found no evidence that intranasal steroids are a cost-effective treatment for OME within the total population of children included within this study. The CUA showed treatment to be dominated by placebo, costing an additional £11 and producing an average of 0.017 fewer QALYs per patient treated. Meanwhile, the CEA showed that there is a 35% risk that treatment is less effective than placebo and that we can be only around 56% confident that treatment is cost-effective, despite a point estimate of £347 per additional case of OME cured. Although it is generally considered appropriate for NHS decision-making to be based primarily on expected net benefits rather than the probability of treatment being cost-effective,[102] the fact that there is no evidence that intranasal steroids significantly improve any clinical outcomes relative to placebo in this population means that the favourable point estimate of the ICER in the CEA must be interpreted with caution alongside evidence on the uncertainty surrounding this finding.

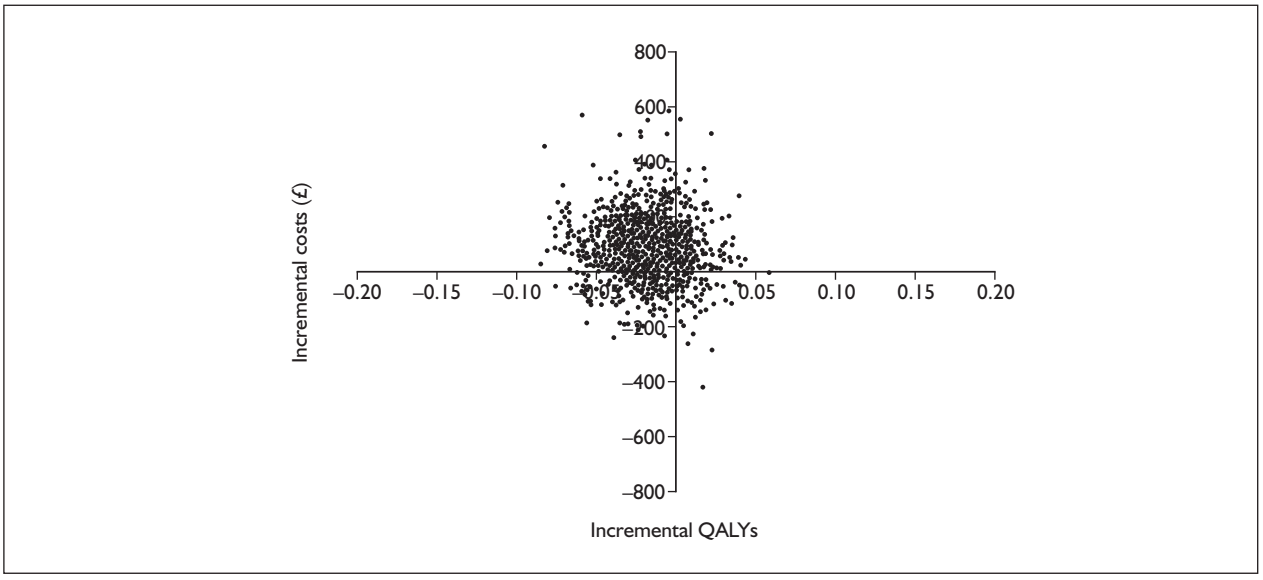

FIGURE 31c *Later trial period without AM: scattergraph showing the distribution of incremental costs and effects for intranasal steroids relative to placebo.*

Furthermore, sensitivity analyses demonstrated that the mean incremental costs and benefits of treatment are sensitive to the assumptions and methods used. However, sensitivity analyses confirmed the finding that there is no evidence for steroids being cost-effective as no sensitivity analyses found the probability of treatment being cost-effective at a £20,000 per QALY ceiling ratio to exceed 89% and none found mean health-care costs to be lower with active treatment than with placebo. Furthermore, no sensitivity analyses found active treatment to be significantly more (or less) effective than placebo or observed a statistically significant difference in costs between two treatment arms based on two-tailed statistical tests.

Both the CEA and CUA highlighted major differences between different age groups. In older children (over 6.5 years), intranasal steroids were found to reduce health-care costs by an average of £152 per child, although there remained a 9% chance that treatment was more costly than placebo. In this age group, treatment was found to have a significantly higher chance than placebo of achieving cure at either 1 or 3 months ($p = 0.0078$ on a one-tailed test), although the CUA demonstrated that the treatment group accrued fewer QALYs than placebo in both age groups. However, it should be noted that the subgroup analyses were not pre-specified and it is possible that the single significant finding of the 24 subgroup analyses conducted may comprise a Type 1 error. Active treatment was also found to have numerically lower mean costs than placebo in girls, children recruited between April and December, children with less severe disease and those who did not have atopy and those who had undergone a period of AM. Conversely, the likelihood of cure was numerically lower for treatment than placebo in younger children, patients with atopy, patients with severe disease and patients recruited between January and March. However, these findings should be interpreted with caution as the differences were marginal and did not reach statistical significance. Furthermore, the treatment group accrued fewer QALYs than placebo in *all* subgroups evaluated.

Chapter 6
Discussion

Main findings

Clinical outcomes

The study is the largest double-blind randomised placebo-controlled trial to date of topical INCS in children with OME, and one of the very few of any type of intervention for OME in primary care where the majority of children continue to be seen. The main findings show that 3 months' use of topical INCS in 4- to 11-year-old children in this setting is no better than placebo in improving clearance of effusions and in improving other important outcomes.

The main study outcome was for efficacy because, while several small studies have suggested efficacy for topical nasal steroids and they are often used off licence for this condition,[61,62,64] efficacy has not yet been demonstrated in the literature. Using objective tympanometric criteria for children cured, the AOR of 0.93 (95% CI 0.50 to 1.75) was not significant. The risk reduction of the treated group calculated for 1-month resolution of bilateral effusions in children rather than ears was –4.3% (95% CI –18.05% to 9.26%). Thus using the upper 95% confidence limit for an effect, we can be confident that a useful effect even as low as 9% increased tympanometric resolution of bilateral glue ear in children is very unlikely in our sample, setting a lower limit for an NNT of 11.

Non-significant secondary outcome efficacy was also found in clearing effusions at 3 and at 9 months. Thus the null hypotheses relating to efficacy that are implicit in the first study aim cannot be rejected for a 3-month course of topical steroid versus placebo for short, medium or longer term efficacy outcomes using clearance of effusions in children.

The most robust and responsive clinical effectiveness outcome currently available, the OM8-30 questionnaire (a condition-specific functional health status measure), also showed negative results at 3 and 9 months. All the substituent eight scales measuring various impacts of the condition on the child's physical health and development showed non-significant differences between treatment arms despite the probability of a false positive outcome. The devised continuous scales would be anticipated to show useful treatment effects of about 0.5 SD, making clinically important false negative effects unlikely.

OM8-30 scales showed recovery profiles, most marked at 3 months (which probably mirrors the tympanometric clearance rates). The fact that the respiratory symptom subscale score, a measure of adenoidal symptoms, was also no different between the allocated arms at 3 months indicates that no other potential treatment benefits than on the ears[103–106] were found. Three-month prospective diary information was also collected for other important continuous variables (collected retrospectively on the OM8-30), such as days with reported otalgia, which was not significantly different between groups at 1 month ($p = 0.43$) nor at 3 months ($p = 0.46$).

Hearing level as an objective outcome is problematic for a primary care study because the gold standard of pure tone audiometry is difficult to perform reliably – particularly in the younger children study and in a community setting where high levels of background noise tend to invalidate the results further. HL as assessed by audiometry is not a known effect modifier and so fail was not set as an inclusion criterion for this study. Four measures of hearing were used but none of these outcomes, although improving over time, showed any significant differences between groups.

The only variable found to affect outcome was clinical severity, based on clinical attendance records and reported frequency of relevant ear problem episodes over the preceding year, age of first episode, bilateral B tympanograms rather than B/C2, and RESP (adenoidal symptom) score. It was noted that by using an age cut-off of 6.5 years, the older children had significantly less severe disease at baseline and so constituted an important subgroup for analysis. Predicted factors such as atopy and season were not significant.

This study has demonstrated the feasibility and acceptability of deploying a 3-month AM scheme (sometimes called watchful waiting) in primary care over which time, and based on a null result, 55%

of children will spontaneously clear the fluid from at least one of their ears and thus considerably reduce their disability risk. This rate of clearance is similar to that found in a Dutch-based primary care and epidemiological study.[30,79] In this study, 72 children were randomised to AM during the first winter periods of the study. Slow recruitment primarily, but also taking into account feedback from children, parents (guardians) and RNs resulted in a DMEC-approved protocol change allowing study entry to children with relevant recent ear problem histories and a single time point fail on tympanometry in both ears (i.e. they did not have to fail tympanometry on two occasions 3 months apart before being randomised to treatment). A sensitivity analysis was performed on the study sample including and excluding the AM group before randomisation, and no significant differences were found for the main tympanometric outcomes at 1 and 3 months, so these populations were subsequently combined in the main analyses. A feature of this study was the rather low referral rate to ENT of just under 15% with 15 cases from the active group and 17 from the placebo group by 9 months. Using MRC-developed referral accuracy criteria, about 60% of the referrals were appropriate, which is relatively high for a condition shown to have a five-fold variability in referral rates. It was uncertain as to what this may be attributed to: the structured AM process, the high reported patient satisfaction with the study, the placebo bias, a Hawthorn effect or various combinations of these. However, it does tend to refute the notion that introducing microtympanometry into primary care would lead to over-referral because it is oversensitive as a diagnostic tool and requires further research of these factors, especially treatment/placebo effects in this setting.

Health economic outcomes

While treatment effects are likely to dissipate rapidly after 3 months, the incomplete natural resolution and relapse rate after 3 months suggest continued NHS resource use with ongoing monitoring in primary care, and referrals should be measured for up to 9 months post randomisation. No studies to date were found that examine these types of longer term outcomes.

The economic evaluation found no evidence that intranasal steroids are cost-effective. However, a non-significant trend towards lower costs in the treatment group than for placebo was observed in older children (over 6.5 years) and children with less severe disease (clinical severity score greater than 0.62). However, these analyses should be interpreted with caution as they were not pre-specified and include small numbers of children. Conversely, analysis of utility instruments found that use of intranasal steroids may reduce children's health-related QoL. The risk of treatment causing harm was particularly pronounced in a number of subgroups: there was found to be a 72% chance that steroids reduce the number of QALYs accrued in older children and a 83% chance in children with severe disease.

Possible reasons for a negative trial

A possible reason for a negative result is that, coming from a primary care sample, the condition was not of sufficient severity in the study sample to anticipate any treatment benefit. There are several reasons why this is highly unlikely. Firstly, the sample of children was selected on NHS use, with children being seen on average twice in the preceding 12 months for otitis media or an ear-related problem. This had to be further confirmed by objective tympanometric criteria with high PPVs of 88% for B and 54% for C2.[71] Children required either B/B or B/C2 to enter. When even stricter criteria were used of a fail on two occasions (B/B, B/C2) 3 months apart before randomisation, a sensitivity analysis on the more persistent sample showed no difference on the null tympanometric outcomes at 1 and 3 months. Sample characteristics were of high baseline severity when compared with the TARGET secondary care trial and higher than the Eurotitis secondary care samples on the baseline OM8-30 score.[5]

If adherence had been poor in the study then this would be an explanation for the negative findings. However, the RNs delivered high-quality interventions in accordance with good adherence principles considering that this was a 3-month delivery of treatment once a day to children as young as 4 years of age. The very high reported adherence (over 90% at 1 month and approaching 90% even by 3 months) was higher than anticipated. An analysis of adherence by age group showed non-significant differences for the main outcome at 1 month, and at 3 months a Fischer's test of $p = 0.04$ showed no linear by linear effects of trend $p = 0.40$ so is probably a chance finding. It is possible, despite the good adherence, that another factor, competence in taking the spray, was higher in the older children and thus affected the outcomes.

The study was associated with high satisfaction levels and a strong placebo effect. However, because the main outcome is measured with little opportunity for bias (problem readings were faxed through for independent interpretation on usability and type, and blinding was total), it is insensitive to placebo effects, so a lack of difference between groups is likely to be real.

The OM8-30 results in particular show strong recovery effects in both groups by 3 months and this may swamp any possible treatment effects. This is a possible explanation but in this case the high natural resolution supports AM without a topical steroid intervention and does not alter the main findings.

The possibility of type 2 error is discussed in Power calculation.

Strengths of the study

The study was set in a UK-wide primary care sample and so should be generalisable to a UK base. There are no relevant contemporary studies in the UK from primary care of interventions likely to be of value in this setting, which is an important one in the management of the majority of children with this condition. The baseline characteristics of the sample are very typical of children seen in primary care with recurrent ear problems, and captures those most likely to benefit from treatment. Children were used as the unit of analysis because the ears are not independent variables and also we wished to use child-centred outcomes.

The main outcomes were robust objective measures and thus added rigour to a condition with a fairly low diagnostic sensitivity and specificity when based on history and otoscopy alone for a primary care sample in which routine overtreatment is likely. Few GPs are skilled in pneumatic otoscopy in the UK and tympanometry gives a high PPV for effusions. The recruitment of affected children was nurse led[107] and all personnel received specific study training and updates including practical sessions on performing tympanometry and audiometry in addition to regular MRC studies training. Independent support for tympanometry was available by telephone and faxing the readings to the co-ordinating centre (University of Southampton). The equipment was calibrated annually throughout the study. Additional local support was provided by the RTNs and quality control visits were performed throughout the study such that each RN received at least three visits from his or her RTN.

Randomisation and concealment

The study was randomised using computer-generated randomisation sequences in which the generator and executor were kept entirely separate. The company supplying the medication mailed the randomisation packs directly to the practices at the start as requested by participating practices. The company had the only copy of the complete randomisation code until all data had been entered on the database and the DMEC authorised unblinding. There were no serious adverse events, and no individual trial code envelopes were opened throughout the trial.

Concealment was evaluated in children and parents (guardians) for which prediction of the correct group was no better than chance. The placebo appeared particularly close to the active treatment as over 80% of parents (guardians) thought their children were receiving the active treatment.

Intention to treat analysis and losses to follow-up

The study data were analysed by group allocated irrespective of treatment received. There was a high level of retention: 93% at 1 month, 83% at 3 months and 75% at 9 months. However, the CONSORT diagram (see *Figure 3*) shows slightly lower levels of retention – 89%, 79% and 66% respectively – as these figures were based upon numbers of children having tympanometry performed at each visit.

The missing data were censored assuming them to be missing at random rather than attempting to impute all missing data for a full ITT. From the data it was not possible to make any informed assumptions about loss to follow-up, e.g. dropouts were better or worse, etc. Thus an ITT analysis is reported with ~90% follow-up for the main outcome at 1 month.

Clinical severity and persistence analyses

Clinical severity analyses found baseline severity to be an outcome but not an effect modifier. The main trial found that any potential treatment effect was in the milder cases which are more likely to resolve naturally, which does not contradict the null result

for use of the intervention. A sensitivity analysis of the cohort plus or minus AM over 3 months, a measure of persistence, did not significantly affect outcomes.

Adherence

Considering the children in the trial were as young as 4 years, the reported adherence at 1 and 3 months was excellent. The original study was intended for children aged 3–11 years but, because of pilot work on nasal sprays in an unreported study, the lower age cut-off was increased to 4 years before the main study was started. Staff training and parent/child interest in the study probably contributed to the high levels of adherence reported in the study, with the possibility of avoiding referral and surgery. However, it is possible that adherence was not as high as reported.

Multiple outcome measures and frequency of follow-up

The study used a wide range of outcome measures and scales other than the main outcome without any statistically significant findings at 1, 3 and 9 months. The study was unusual in following a non-surgical intervention over a longer time frame necessary to establish cost-effectiveness.

Limitations of the study

The study contained a large number of outcome measures (see Chapter 2 and appendices) and so the prior probability of a type 1 error was very high. However, even on full analysis, no significant positive outcomes were found. This study was also clearly reported in relation to the protocol analysis plan (version 3, dated 5 May 2005) to avoid any, in this instance, unnecessary Bonferroni corrections. Thus while so many outcomes constitute a structural weakness of the study, it is a hypothetical weakness only.

Although a number of aspects of data collection and recruitment criteria were amended in a protocol modification, a subgroup efficacy analysis found that the AM group was not significantly different to the no AM group and so has not affected the main results. Furthermore, changes to the parental resource use questionnaire that were made during the protocol amendment had no effect on the base-case economic evaluation, which used retrospective cost collection from children's medical records. However, the late introduction of utility measures (which were not collected prior to the protocol amendment) did result in around one-third of children having missing utility data in addition to some missing utility data arising from non-completion of questionnaires. In the base-case analysis, missing data were imputed using multiple imputation techniques, although a wide range of alternative imputation methods were investigated and found to have no influence on the conclusions.

Recruitment, sample characteristics and generalisability

The recruitment numbers per practice were higher than the average RCT performed in primary care, although not excessively so.[108] The method of RN recruitment and exclusion of non-recruiting practices on steering group review probably contributed to this. Use of audits with invitation for tympanometry more accurately identified a population in primary care for treatment than is usually the case, so in this sense may not be generalisable to actual practice where treatments may be given with less certainty of accurate diagnosis. Use of audits was necessary to ensure systematic patient identification using a nurse-led system. The opportunistic referrals constituted 12% of the study population and behaved no differently in terms of tympanometric outcomes. In addition, the population is typical of primary care because all children had presented to the doctor with an otitis media or ear problem episode, on average, on two occasions in the previous year, which is typical of primary care practice.[1] It is possible that targeted screening, although presumably only affected children and families responded to invitation, may have been over-inclusive for actual practice presentations. However, this effect was probably negated by the high numbers of actual fails. Tympanometry use does limit current generalisability to normal practice in which probably only about 5% of practices have a tympanometer on site. Some practices approached may also have found this procedure unacceptable as a routine. However, it is argued that the PPV of clinical symptoms and signs in diagnosis of OME in primary care is so low that meaningful results relating to efficacy of treatment for the target condition of OME could not be gained without its use.

Interestingly, relatively few of the children attending screening had bilateral OME confirmed and considering unilateral OME has little attendant probable disability, this underlines the

value of assessing both ears in primary care prior to treatment decisions (and NHS resource use). Given the large numbers of children actually screened per practice, the relatively few being randomised (see *Figure 3*) were not therefore likely to be atypical of children requiring or needing treatment in a primary care setting, and indeed represent an appropriate group for treatment. It could be argued that the study sample was not sufficiently severe and showed only natural recovery effects in both groups. However, as an RCT such confounders should be and in fact were evenly distributed. The older children (over 6.5 years) showed less severity at baseline and so constituted an interesting subgroup for any treatment effect, which has to be weighed against natural resolution effects. In this sense, clinical opinion could remain very important here because some such older children may also have had immune problems and these may filter through more to secondary care.

Primary care is not the only setting where topical steroids may be used and, indeed, off-licence use of topical steroids in ENT departments is likely to be substantial. As a primary care sample the results may not be generalisable to secondary care; however, the high equivalent baseline OM8-30 score in particular tends to suggest that results would be no different in a secondary care sample. Also the resolution rates of about 50% are similar to those observed in secondary care, thus supporting generalisability of findings to similar secondary care populations.

Power calculation

Two hundred and forty children were required, assuming a 15% dropout rate and 3% non-interpretable rate for an alpha of 0.05 and a beta of 0.2 and assuming 28% tympanometric resolution in the topical steroid group and 12% in the placebo group.[19] Differences of 15% or less for tympanometric outcomes are not likely to be clinically significant as tympanometry is a disease measure with only a moderate PPV of 0.49[80,81] for a relevant clinical outcome – the pure tone hearing level. Although only 217 children were in fact recruited, an end-of-study analysis by the DMEC found that the study had achieved a meaningful negative trial finding in relation to the primary outcome. With an NNT of 11 or more, clinically important effects are not likely to be present in the population from which the study sample came.

A larger sample size is always desirable. The number of children randomised could have been much larger if less stringent inclusion criteria had been applieds and more outcome data would have been available if a by-ear rather than by-child analysis had been applied. This study sample used a more generous but equally rigorous and widely accepted definition of cure than the study used for the original power calculation (type A only) which excluded proportions of about 30% higher resolution to type CI tympanograms, generally considered normal and used in other primary care studies.[79]

Much higher proportions of treated and control children resolving were observed in this study sample than in the American sample[60] because of our revised tympanometric criteria (A/C1 = cure) and may be attributed also to spectrum bias (not able to be considered in the original calculation assumptions).

Chapter 7
Conclusion

Implications for practice

The null main findings showed, with confidence, that the use of topical INCS in children with OME is not worthwhile because the NNT for a 1-month course of nasal steroids exceeds 11, indicating lack of useful efficacy. Additionally, 7–22% of treated patients experienced side effects. At the same time, study documentation of the natural history of OME in this setting with strong placebo effects noted (80% from both groups thought they had received active treatment) suggest the utility of AM supported by an effective medical treatment. The main implications are:

- Topical INCS are very unlikely to be an effective or worthwhile treatment for OME in primary care.
- This is also likely to be the case in secondary care because baseline sample characteristics were similar on the OM8-30 and resolution rates were similar.
- AM in primary care for children with OME is acceptable and satisfactory to children and families but the technology and methods used may require adaptation.[16,101]
- Relatively few children with histories of ear problems attending the GP surgery have bilateral OME confirmed using an objective test and thus need treatment.
- AM in primary care results in high satisfaction and low referral rates, but may in part be due to placebo effects.

Implications for research

This large study of topical nasal steroids in a primary care population with null effect suggests that further studies, particularly in primary care populations, would not be worthwhile. However, a potential effect in children older than 6.5 years may be further evaluated. Because Cochrane has identified steroids as of potential benefit[9] and theoretical work continues to support this,[58,97] the role of oral steroids may also be profitably explored. However, because of the potential harms of oral steroids and with possible effects on growth and severe idiosyncratic reactions,[2] their research use should be confined to secondary care and to targeted populations only (e.g. subgroups of particular interest, such as those with moderate to severe allergies) or as an alternative to reinsertion of grommets in older children, etc. The use of oral steroids is not recommended for a condition with this type of resolution/protracted natural history in primary care, and there are currently no or very limited predictors of outcome and treatment benefit.

Future research

The main recommendation for primary care research, based on the fact that very high satisfaction and low referral levels can be achieved through the use of a non-surgical intervention with AM, is to evaluate other interventions in primary care in a similar fashion. Perhaps the highest level of priority should be given to mechanical rather than medical interventions to achieve this, using purpose-built auto-inflation devices and standardised techniques.[4,44,45] A study using a similar RCT design and objective outcomes as presented here but without concealment could usefully be performed, and analysing effects of younger versus older age along with severity. Such a study could be combined with an evaluation of different feasible diagnostic methods of OME in primary care along with tympanometry to improve likely uptake of AM more generally in practices that do not opt to use nurse-led tympanometry as a means of monitoring and decision-making.

Acknowledgements

We wish to acknowledge and thank the following people and organisations.

Firstly, our thanks to all the children and parents who helped and were a vital part of this study. We also thank the Medical Research Council General Practice Research Framework for its major contribution.

We are grateful particularly to Mark Haggard for providing the OM8-30 instrument and help with the analysis of it and other suggestions, and also Helen Spencer. We also wish to express appreciation of Gerry Leydon for her qualitative advice of the exit interviews. We thank Gilly O'Reilly for her able cover during Sarah Benge's maternity leave.

Thanks particularly to Martin Burton, Anthony Harnden, Chris Frost and Paul Scarnell for their time, skills and advice as part of the TSC, and also Bob Walton and Ian White of the DMEC.

We thank Sharon Charnock of Starkey Laboratories for the provision of the trial microtympanometers, and her and the company's involvement in the many training days at the MRC London. We also thank the Medicines for Children Research Network for their adoption of the study and indirect support, and Mr Peter Robb for his timely ENT advisor comments.

We thank Schering-Plough for provision of all trial supplies of mometasone and placebo, and assistance with the randomisation.

Finally, considered and considerable thanks to the HTA programme for providing the research funding and the NHS R&D for providing excess treatment funding and service support costs for research nurses and practices.

Contribution of authors

Dr Ian Williamson (Senior Lecturer in Primary Care) contributed to the conception, design, analysis, interpretation and report, and Dr Sarah Benge (Research Fellow) to the design, data collection, analysis and report. Ms Sheila Barton (Senior Research Fellow, Statistician) contributed to the analysis and report. Dr Stavros Petrou (Senior Research Officer, Health Economist) contributed to the design, analysis, interpretation and report. Louise Letley (Senior Nurse Manager, MRC GPRF) and Nicky Fasey (Senior Research Nurse, MRC GPRF) contributed to the conception, design and report. Giselle Abangma (Research Officer, Health Economist) and Helen Dakin (Research Officer, Health Economist) contributed to the analysis, interpretation and report. Professor Paul Little (Professor of Primary Medical Care) contributed to the conception design and report.

References

1. Williamson I, Benge S, Mullee M, Little P. Consultations for middle ear disease, antibiotic prescribing and risk factors for re-attendance: a case linked cohort study. *Br J Gen Pract* 2006;**56**:170–5.

2. Williamson I. Otitis media with effusion. *BMJ Clin Evid* 2002;**7**:469–76.

3. DOH. *Hospital Episode Statistics. Grommets.* (D15) Department of Health; 2004 (and website 2006/7). www.dh.gov.uk/PublicationsandStatistics/Publications/PublicationsStatistics/DH_066322. Last accessed June 2009.

4. NICE. *Surgical management of otitis media with effusion in children.* NICE Clinical Guideline 60; 2008. URL: www.nice.org.uk/usingguidance/implementationtools/costingtools/costing_tools.jsp. Last accessed February 2008.

5. Haggard M. (MRC Cambridge, 2008, personal communication) and ESPO 8th International Conference Proceedings, Budapest, June 2008 (abstract 550PI-4).

6. Wilmot JF. Persistent effusion following acute otitis media: tympanometry and pneumatic otoscopy in diagnosis. *Br J Gen Pract* 1988;**38**:149–52.

7. Freemantle N, Long A, Mason J, Sheldon T, Song F, Watson P, *et al*. The treatment of persistent glue ear in children. *Effective Health Care Bulletin* 1992;**4**:1–15.

8. Mason J, Freemantle N, Browning G. Impact of Effective Health Care bulletin on treatment of persistent glue ear in children: time series analysis. *BMJ* 2001;**323**:1096–7.

9. Butler CC, van der Voort JH. *Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children.* Cochrane Library, Issue 2; 2002. Oxford: Update Software.

10. Lous J, Burton M, Felding J, Ovesen T, Rovers MM, Williamson I. *Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children.* Cochrane Library, Issue 1; 2005. Chichester: John Wiley & Co.

11. Griffin GH, Flynn C, Bailey RE, Schultz JK. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. *Cochrane Database Syst Rev* 2006; Issue 4, Art. No.: CD003423. DOI:10.1002/14651858.CD003423.pub2.

12. Cantekin EI, McGuire TW. Antibiotics are not effective for otitis media with effusion: reanalysis of meta-analysis. *Otorhinolaryngol Nova* 1998;**8**:136–47.

13. Haggard M, Hughes E. *Screening children's hearing: a review of the literature and implications of otitis media.* London: HMSO; 1991.

14. Haggard MP, Smith SC. Impact of otitis media on child quality of life. In Rosenfeld RM, Bluestone CD, editors. *Evidence based otitis media.* St. Louis, MO: B.C.Decker Inc.; 1999: 375–98.

15. Bennett KE, Haggard MP, Silva PA, Stewart IA. Behaviour and development effects of otitis media with effusions into the teens. *Arch Dis Child* 2001;**85**:91–5.

16. Browning GG. Watchful waiting in childhood otitis media with effusion. *Clin Otolaryngol Allied Sci* 2001;**26**:263–4.

17. Browning GG. Two-year outcome of ventilation tubes in a randomized controlled trial of persistent otitis media with effusion. *Clin Otolayngol Allied Sci* 2001;**26**:342–4.

18. Hogan SC, Stratford KJ, Moore DR. Duration and recurrence of otitis media with effusion in children from birth to 3 years: prospective study using monthly otoscopy and tympanometry. *BMJ* 1997;**314**:350–3.

19. Williamson IG, Dunleavey J, Bain J, Robinson D. The natural history of otitis media with effusion – a three year study of the incidence and prevalence of abnormal tympanograms in four South West Infant and first schools. *J Laryngol Otol* 1994;**108**:930–4.

20. Zielhuis GA, Rach GH, Broek PV. Screening for otitis media with effusion in preschool children. *Lancet* 1989;**1**:311–14.

21. Rosenfeld RM, Goldsmith AJ, Tetlus L, Balzano A. Quality of life for children with otitis media. *Arch Otolaryngol Head Neck Surg* 1997;**123**:1049–54.

22. Casselbrant ML, Brostoff LM, Cantekin EI, Flaherty MR, Doyle WJ, Bluestone CD, *et al*. Otitis media with effusion in preschool children. *Laryngoscope* 1985;**95**:428–36.

23. Williamson I, Little P. Otitis media with effusion: the long and winding road? *Perspective Arch Dis Child* 2008;**93**;268–9.

24. Williamson IG, Sheridan C, Galker E, Lous J. A video-based performance in noise test for measuring audio-visual disability in young school children: test development, with validation by trained teachers, parents and audiometry as relative standards for disability. *Int J Pediatr Otorhinolaryngol* 1999;**49**:127–33.

25. Paradise JL, Feldman HM, Campbell TF, Dollaghan CA, Rockette HE, Pitcairn DL, *et al*. Tympanostomy tubes and developmental outcomes at 9 to 11 years of age. *N Engl J Med* 2007;**356**:248–61.

26. Moore DR, Hartley DE, Hogan SC. Effects of otitis media with effusion on central auditory function. *Int J Paed Otorhinolaryngol* 2003;**67**:S63–7.

27. Maw AR. Children with glue-ear: how do they present? *Clin Otolaryngol Allied Sci* 1988;**13**:171–7.

28. Toner JG. Pneumatic otoscopy and tympanometry in the detection of middle ear effusion. *Clin Otolaryngol Allied Sci* 1990;**15**:121–3.

29. Bennett KE, Haggard MP, Churchill R, Wood S. Improving referrals for glue-ear from primary care. *J Health Serv Res Policy* 2001;**6**:139–44.

30. Anteunis LJ, Engel JA, Hendriks JJ, Manni JJ. A longitudinal study of the validity of parental reporting in the detection of otitis media and related hearing impairment in infancy. *Audiology* 1999;**38**:75–82.

31. Van Balen FA, de Melker RA. Validation of a portable tympanometer for use in primary care. *Int J Pediatr Otorhinolaryngol* 1994;**29**:219–25.

32. Maw AR. Using tympanometry to detect glue ear in general practice. Editorial. *BMJ* 1992;**304**:67–8.

33. Rovers M, Black N, Browning G, Maw R, Zielhuis GA, Haggard MP. Grommets in otitis media with effusion: an individual patient data meta-analysis. *Arch Dis Child* 2005;**90**:480–5.

34. van Balen FA. *Otitis media with effusion in general practice.* MD Thesis 1995. University of Utrecht.

35. Williamson IG, Dunleavey J, Robinson D. Risk factors in otitis media with effusion: a 1 year case control study in 5–7 year old children. *Fam Pract* 1994;II:271–4.

36. Browning GG. Evidence based advice for glue ear. *Practitioner* 2003;**247**:626–34.

37. Goossens H, Ferech M, Vander SR, Elseviers M. Outpatient antibiotic use in Europe and its association with resistance: a cross-national database study. *Lancet* 2005;**365**(9459):579–87.

38. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomized controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;**332**:336–42.

39. Little P, Moore M, Warner G, Gould C, Dunleavey J, Williamson I. Predictors of poor outcome and benefit from antibiotics in children with acute otitis media: pragmatic randomized trial. *BMJ* 2002;**325**:22–5.

40. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross-sectional prevalence study. *BMJ* 1996;**313**:387–91.

41. Guillemot D, Carbon C, Balkau B, Geslin P, Lecouer H, Vauzelle-Kervroedan F, *et al*. Low dose and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. *JAMA* 1998;**279**:365–70.

42. Pichichero ME, Casey JR. Emergence of multiresistant serotype 19A pneumococcal strain not included in the 7 valent conjugate vaccine as an otopathogen in children. *JAMA* 2007;**298**:1772–8.

43. Griffin GH, Flynn C, Bailey RE, Schultz JK. Antihistamines and or decongestants for otitis media with effusion (OME) in children. *Cochrane Database Syst Rev* 2006; Issue 4, Art. No.: CD003423. DOI:10.1002/146511858.CD0033423.pub2.

44. Reidpath DD, Glasziou PP, Del Mar C. Systematic review of autoinflation for treatment of glue ear in children. *BMJ* 1999;**318**:1177–8.

45. Perera R, Haynes J, Glasziou P, Heneghan CJ. Autoinflation for hearing loss associated with otitis media with effusion (Cochrane Review). *Cochrane Database Syst Rev* 2006; Issue 4, Art No.: CD006285.

46. Berman S, Roark R, Luckey D. Theoretical cost-effectiveness of management options for children with persisting middle ear effusions. *Am Acad Pediatr* 1994;**93**:353–63.

47. *British national formulary 39*; 2000.

48. Berman S, Grose K, Nuss R, Huber-Navin C, Roark R, Gabbard SA, *et al*. Management of chronic middle ear effusion with prednisolone combined with trimethoprim-sulfamethoxazole. *Pediatric Infect Dis J* 1990;**9**:533–8.

49. Macknin ML, Jones PK. Oral dexamethasone for treatment of persistent middle-ear effusion. *Pediatrics* 1985;**75**:329–35.

50. Hemlin C, Carenfelt C, Papatziamos G. Single dose of betamethasone in combined medical treatment

of secretory otitis media. *Ann Otol Rhinol Laryngol* 1997;**106**:359–63.

51. Lambert P. Oral steroid therapy for chronic middle ear perfusion: a double blind cross-over study. *Otolaryngol Head Neck Surg* 1986;**95**:193–9.

52. Niederman LG, Walter-Bucholtz V, Jabalay T. A comparative trial of steroids versus placebos for treatment of chronic otitis media with effusion. In Lim D, Bluestone C, editors. *Recent advances in otitis media*. St. Louis, MO: BC Decker Inc.; 1984: 273–5.

53. Schwartz RH, Puglese J, Schwartz DM. Use of a short course of prednisone for treating middle ear effusion: a double blind cross over study. *Ann Otol Rhinol Laryngol* 1980;**89**(Suppl. 68):296–300.

54. Podoshin L, Fradis M, Ben-David Y, Farragi D. The efficacy of oral steroids in the treatment of persistent otitis media with effusion. *Arch Otolaryngol Head Neck Surg* 1990;**116**:1404–6.

55. Giebink GS, Batalden PB, Le CT, Lassman FM, Buran DJ, Seltz AE. A controlled trial comparing three treatments for chronic otitis media with effusion. *Pediatr Infect Dis J* 1990;**9**:33–40.

56. Persico M, Podoshen L, Fradis M. Otitis media with effusion: a steroid and antibiotic therapeutic trial before surgery. *Ann Otol Rhinol Laryngol* 1978;**87**:191–6.

57. Berman S, Grose K, Zerbe GO. Medical management of chronic middle-ear effusion. *Am J Dis Child* 1987;**141**:690–4.

58. Yaman H, Ozturk K, Uyar Y, Gurbilek M. Effectiveness of corticosteroids in otitis media with effusion: an experimental study. *J Laryngol Otol* 2008;**122**:25–30.

59. Rosenfeld RM, Mandel EM, Bluestone CD. Systemic steroids for otits media with effusion in children. *Arch Otolaryngol Head Neck Surg* 1991;**117**:984–9.

60. Tracy JM, Demain JG, Hoffman KM, Goetz DW. Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion. *Ann Allergy Asthma Immunol* 1998;**80**:198–206.

61. Fokkens WJ, Scadding GK. Perennial rhinitis in the under 4s: a difficult problem to treat safely and effectively? A comparison of intranasal fluticasone proprionate and ketotifen in the treatment of 2–4 year old children with perennial rhinitis. *Pediatr Allergy Immunol* 2004:**15**:261–6.

62. Shapiro GG, Bierman CW, Furukuwa CT, Pierson WE, Berman R, Donaldson J, *et al*. Treatment of persistent Eustachian tube dysfunction with aerosolized nasal dexamethasone phosphate versus placebo. *Ann Allergy* 1982;**80**:198–206.

63. Cengel S, Akyol MU. The role of topical nasal steroids in the treatment of children with otitis media with effusion and/or adenoid hypertrophy. *Int J Pediatr Otorhinolaryngol* 2005;**70**:639–45. doi:10.1016/j.ijporl.2005.08.013.

64. The use of inhaled corticosteroids in childhood asthma. *Drugs Therapeutics Bull* 1999;**37**(10):73–7.

65. Barek PJ, Bergman DA, Ducharme F. Beclomethasone for asthma in children: effects on linear growth. *Cochrane Database Syst Rev* 1999; Issue 3, Art. No.: CD001282. DOI:10.1002/14651858. CD001282.

66. Shenkel EJ, Skoner DP, Bronsky EA, Miller D, Pearlman D, Rooklin A, *et al*. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics* 2000;**105**:2.e22

67. Skoner DP, Rachelefsky MD, Meltzer EO, Chervinsky P, Morris RM, Seltzer JM, *et al*. Detection of growth suppression in children during treatment with intranasal beclomethasone diproprionate. *Pediatrics* 2000;**105**:2.e23.

68. *Nasonex Aqueous Nasal Spray. Product Information Sheet.* Last update on eMC: 2001. Schering-Plough Ltd.

69. Jerger J. Clinical experience with impedance audiometry. *Arch Otolaryngol* 1970;**92**:311–24.

70. Fiellau-Nikolajsen M. Epidemiology of secretory otitis media: a descriptive cohort study. *Ann Otol Rhinol Laryngol* 1983;**92**:311–24.

71. Cantekin EI, Bluestone CD, Fria TJ, Stool SE, Berry QC, Sabo DL. Identification of otitis media with effusion in children. *Ann Otol Rhinol Laryngol* 1980;**899**(S68):190–5.

72. Hennessy S, Kind P. *Measuring health status in children*: *developing and testing a child-friendly version of EQ-5D.* Proceedings of the 19th plenary meeting of the EuroQol Group York, UK, 13th–14th September 2002. 2002:291–310.

73. Kind P, Macran S. *Levelling the playing field*: *Increasing the number of response categories in EQ-5D.* Proceedings of the 19th plenary meeting of the EuroQol Group York, UK, 13th–14th September 2002. 2002:311–22.

74. Janssen MF, Birnie E, Bonsel GJ. Quantification of the level descriptors for the standard EQ-5D three-

level system and a five-level version according to two methods. *Qual Life Res* 2008;**17**:463–73.

75. Janssen MF, Birnie E, Haagsma JA, Bonsel GJ. Comparing the standard EQ-5D three-level system with a five-level version. *Value Health* 2008;**11**:275–84.

76. Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. *Med Care* 2007;**45**:259–63.

77. Pickard AS, Kohlmann T, Janssen MF, Bonsel G, Rosenbloom S, Cella D. Evaluating equivalency between response systems: application of the Rasch model to a 3-level and 5-level EQ-5D. *Med Care* 2007;**45**:812–19.

78. Jenkins L, Britten N, Barber N, Bradley C. *Resource pack for reviewing and monitoring prescribing*. Draft 3.1. Presented prescribing conference, Exeter University; 2002.

79. van Balen FAM, de Melker RA, Touw-Otten FW. Double blind randomised trial of co-amoxiclav versus placebo for persistent otitis media with effusion in general practice. *Lancet* 1996;**348**:713–16.

80. Dempster JH, MacKenzie K. Tympanometry and the detection of hearing impairment associated with otitis media with effusion. *Clin Otolaryngol* 1991;**16**:157–9.

81. Stool SE, Berg AO, Berman S, Carney CT, Cooley JR, Culpepper L, *et al*. *Otitis media with effusion in children*. Guideline Technical Report no. 12 AHCPR Publication No. 95–0621 Rockville MD: Agency for Health Care policy and Research, Public Health Services US Department of Health and Human Services; 1994.

82. Petrou S, Murray L, Cooper P, Davidson LL. The accuracy of self-reported healthcare resource utilization in health economic studies. *Int J Technol Assess Health Care* 2002;**18**:705–10.

83. Drummond MF. *Methods for the economic evaluation of health care programmes*. 3rd edn. Oxford: Oxford University Press; 2005.

84. Netten A, Curtis L. *Unit costs of health and social care*. Canterbury: Personal Social Service Research Unit: University of Kent; 2006.

85. Department of Health. *NHS reference costs 2006*. London: Department of Health; 2006.

86. *British national formulary 54*; 2007.

87. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, *et al*. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Med Care* 2002;**40**:113–28.

88. Furlong W, Feeny D, Torrance GW, Goldsmith CH, DePauw S, Zhu Z, *et al*. *Multiplicative multi-attribute utility function for the health utilities index Mark 3 (HUI3) system*: *A technical report*. CHEPA Working Paper Series 98–11. 1998.

89. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108.

90. Cox CL, Lensing S, Rai SN, Hinds P, Burghen E, Pui CH. Proxy assessment of quality of life in pediatric clinical trials: application of the Health Utilities Index 3. *Qual Life Res* 2005;**14**:1045–56.

91. Eiser C, Morse R. The measurement of quality of life in children: past and future perspectives. *J Dev Behav Pediatr* 2001;**22**:248–56.

92. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. *Arch Dis Child* 2001;**84**:205–11.

93. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;**14**:487–96.

94. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing... presumed at random: cost-analysis of incomplete data. *Health Econ* 2003;**12**:377–92.

95. Yu LM, Burton A, Rivero-Arias O. Evaluation of software for multiple imputation of semi-continuous data. *Stat Methods Med Res* 2007;**16**:243–58.

96. Hogan SC, Stratford KJ, Moore DR. Duration and recurrence of otitis media with effusion in children from birth to 3 years: prospective study using monthly otoscopy and tympanometry. *BMJ* 1997;**314**:350–3.

97. Lothgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. *Health Econ* 2000;**9**:623–30.

98. *Key Demographic Statistics From UK General Practice*. URL: www.rcgp.org.uk/pdf/ISS_FACT_06_KeyStats.pdf. Last accessed 2003.

99. Morgan O, Baker A. *Measuring deprivation in England and Wales using 2001 Carstairs scores*. National Statistics Quarterly No. 31. 2006.

100. Department of Health. *Payment by results*: *National Tariff for 2006*. London: Department of Health; 2007. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_127649. Last accessed 11 June 2009.

101. National Institute for Health and Clinical Excellence. *Surgical management of OME: Costing template. Implementing NICE guidance.* NICE Clinical Guideline 60. 2008. URL: www.nice.org.uk/nicemedia/pdf/SurgicalManagementOfOMECostingTemplate.xls. Last accessed March 2008.

102. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999;**18**:341–64.

103. Demain JG, Goetz DW. Paediatric adenoidal hypertrophy and nasal airway obstruction; reduction with aqueous nasal beclomethasone. *Pediatrics* 1995;**95**:355–64.

104. Lepcha A, Kurien M, Job A, Thomas K. Chronic adenoid hypertrophy in children – is steroid nasal spray beneficial? *Indian J Otolaryngol Head Neck Surg* 2002;**54**:280–4.

105. Criscuolii G, D'Amora S, Ripa G, *et al*. Frequency of surgery among children who have adenotonsillar hypertrophy and improve after treatment with nasal beclomethasone. *Pediatrics* 2003;**111**:e236–8.

106. Berluchi M, Salsi D, Valetti L, *et al*. The role of mometasone furoate aqueous nasal spray in the treatment of adenoidal hypertrophy in the pediatric age group: preliminary results of a prospective randomised study. *Pediatrics* 2007;**119**:e1392–7.

107. Fall M, Walters S, Deverill M, *et al*. An evaluation of a nurse-led ear care service in primary care: benefits and costs. *Br J Gen Pract* 1997;**47**:699–703.

108. Wilson S, Delaney B, Roalfe A, *et al*. Randomised controlled trials in primary care: case study. *BMJ* 2000;**321**:24–27.

109. Timmerman AA, Meesters CM, Speyer R, Anteunis LJ. Psychometric qualities of questionnaires for the assessment of otitis media impact. *Clin Otolaryngol* 2007;**32**:429–39.

110. Timmerman AA, Meesters CM, Anteunis LJ, Chenault MN, Haggard MP. Psychometric evaluation of the OM8-30 questionnaire in Dutch children with otitis media. *Eur Arch Otorhinolaryngol* 2008;**265**:1047–56.

111. Haggard M, Spencer H, Gregori M. Internationally standardised clinical description: can it be achieved ENT? *ENT News* 2007;**16**:69–72.

112. Medical Research Council Multicentre Otitis Media Study Group. Influence of age, type of audiometry and child's concentration on hearing thresholds. *Br J Audiol* 2000;**34**:231–40.

113. Medical Research Council Multicentre Otitis Media Study Group. 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 Allied Sci* 2001;**26**:417–24.

114. Medical Research Council Multicentre Otitis Media Study Group. Sensitivity, specificity and predictive value of tympanometry in predicting a hearing impairment in otitis media with effusion. *Clin Otolaryngol Allied Sci* 1999;**24**:294–300.

115. Haggard M, Spencer H, Gregori M. OM8-30 for assessment and outcome in OME: origins, applications & ultra-short OM2–13, revised Autumn 2006.

116. Medical Research Council Multicentre Otitis Media Study Group. Air-conduction estimates from tympanometry (ACET) 1: relationship to measured hearing in OME. *Int J Pediatr Otolaryngol* 2009;in press.

117. StataCorp. Regress – linear regression. Stata Base Reference Manual: 2007;Release 10:79–101. College Station, TX: StataCorp LP.

118. StataCorp. 20.15: Obtaining robust variance estimates. Stata Base Reference Manual: 2007;Release 10:268–73. College Station, TX: StataCorp LP.

119. Brazier JE, Yang Y, Tsuchiya A. *A review of studies mapping (or cross walking) from non-preference based measures of health to generic preference-based measures.* The University of Sheffield, Health Economics and Decision Science Discussion Paper Series 2008;08/02:A033. URL: www.shef.ac.uk/content/1/c6/01/87/47/HEDS%20DP%200802pdf. Last accessed 1 July 2008.

120. Zielhuis GA, Rach GH, van den Broek P. Screening for otitis media with effusion in preschool children. *Lancet* 1989;**1**:311–14.

121. Grutters JP, Joore MA, van der Horst F, Verschuure H, Dreschler WA, Anteunis LJ. Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Qual Life Res* 2007;**16**:1439–49.

122. National Statistics. *Prescription cost analysis: England, 2006*. URL: www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-2006. Last accessed December 2007.

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al*.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al*.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al*.

No. 31
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al*.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al*.

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*.

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

No. 3
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al*.

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*.

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al*.

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.
By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al*.

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al*.

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al.*

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al.*, on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, *et al.*

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, *et al.*

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al.*

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, *et al.*

No. 20
Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, *et al.*

No. 21
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).
By Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, *et al.*

No. 22
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study.
By Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, *et al.*

No. 23
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.
By Bryant J, Cooper K, Picot J, Clegg A, Roderick P, Rosenberg W, *et al.*

No. 24
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis.
By McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K, *et al.*

No. 25
Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).
By Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, *et al.*

No. 26
A systematic review of presumed consent systems for deceased organ donation.
By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

No. 27
Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial.
By Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, *et al.*

No. 28
A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).
By Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al.*

No. 29
Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making.
By Andronis L, Barton P, Bryan S.

Suppl. 1
Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal.
By Ward S, Pilgrim H, Hind D.

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal.
By Chilcott J, Lloyd Jones M, Wilkinson A.

The use of paclitaxel in the management of early stage breast cancer.
By Griffin S, Dunn G, Palmer S, Macfarlane K, Brent S, Dyker A, *et al.*

Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma.
By Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, *et al.*

Bortezomib for the treatment of multiple myeloma patients.
By Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, *et al.*

Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.
By Walker S, Palmer S, Erhorn S, Brent S, Dyker A, Ferrie L, *et al.*

Erlotinib for the treatment of relapsed non-small cell lung cancer.
By McLeod C, Bagust A, Boland A, Hockenhull J, Dundar Y, Proudlove C, *et al.*

Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.
By Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, *et al.*

Infliximab for the treatment of adults with psoriasis.
By Loveman E, Turner D, Hartwell D, Cooper K, Clegg A.

No. 30
Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trial.
By Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, *et al*.

No. 31
The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.
By Rogowski R, Burch J, Palmer S, Craigs C, Golder S, Woolacott N.

No. 32
Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.
By Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, *et al*.

No. 33
A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.
By Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al*., on behalf of the 3CPO study investigators.

No. 34
Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.
By Ara R, Pandor A, Stevens J, Rees A, Rafia R.

No. 35
Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.
By Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al*.

No. 36
Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.
By Hewitt CE, Gilbody SM, Brealey S, Paulden M, Palmer S, Mann R, *et al*.

Health Technology Assessment programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Observers

Diagnostic Technologies & Screening Panel

Members

Chair,
Professor Paul Glasziou,
Professor of Evidence-Based Medicine, University of Oxford

Deputy Chair,
Dr David Elliman,
Consultant Paediatrician and Honorary Senior Lecturer, Great Ormond Street Hospital, London

Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, Imaging Science and Biomedical Engineering, Cancer & Imaging Sciences, University of Manchester

Ms Jane Bates, Consultant Ultrasound Practitioner, Ultrasound Department, Leeds Teaching Hospital NHS Trust

Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales

Dr Ron Gray, Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford

Professor Paul D Griffiths, Professor of Radiology, University of Sheffield

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Dr Anne Mackie, Director of Programmes, UK National Screening Committee

Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr W Stuart A Smellie, Consultant in Chemical Pathology, Bishop Auckland General Hospital

Dr Nicholas Summerton, Consultant Clinical and Public Health Advisor, NICE

Ms Dawn Talbot, Service User Representative

Dr Graham Taylor, Scientific Advisor, Regional DNA Laboratory, St James's University Hospital, Leeds

Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

Observers

Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health

Dr Catherine Moody, Programme Manager, Neuroscience and Mental Health Board

Dr Ursula Wells, Principal Research Officer, Department of Health

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Deputy Chair,
Professor Imti Choonara,
Professor in Child Health, University of Nottingham

Mrs Nicola Carey, Senior Research Fellow, School of Health and Social Care, The University of Reading

Mr John Chapman, Service User Representative

Dr Peter Elton, Director of Public Health, Bury Primary Care Trust

Dr Ben Goldacre, Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London

Mrs Barbara Greggains, Service User Representative

Dr Bill Gutteridge, Medical Adviser, London Strategic Health Authority

Dr Dyfrig Hughes, Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University

Professor Jonathan Ledermann, Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre

Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Professor Femi Oyebode, Consultant Psychiatrist and Head of Department, University of Birmingham

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge

Dr Martin Shelly, General Practitioner, Leeds, and Associate Director, NHS Clinical Governance Support Team, Leicester

Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Mr David Symes, Service User Representative

Dr Lesley Wise, Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines & Healthcare Products Regulatory Agency

Observers

Ms Kay Pattison, Section Head, NHS R&D Programme, Department of Health

Mr Simon Reeve, Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health

Dr Heike Weber, Programme Manager, Medical Research Council

Dr Ursula Wells, Principal Research Officer, Department of Health

Current and past membership details of all HTA programme 'committees' are available from the HTA website (www.hta.ac.uk)

Therapeutic Procedures Panel

Members

Chair,
Dr John C Pounsford,
Consultant Physician, North Bristol NHS Trust

Deputy Chair,
Professor Scott Weich,
Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry

Professor Jane Barlow,
Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry

Ms Maree Barnett,
Acting Branch Head of Vascular Programme, Department of Health

Mrs Val Carlill,
Service User Representative

Mrs Anthea De Barton-Watson,
Service User Representative

Mr Mark Emberton,
Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London

Professor Steve Goodacre,
Professor of Emergency Medicine, University of Sheffield

Professor Christopher Griffiths,
Professor of Primary Care, Barts and The London School of Medicine and Dentistry

Mr Paul Hilton,
Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne

Professor Nicholas James,
Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital

Dr Peter Martin,
Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Dr Kate Radford,
Senior Lecturer (Research), Clinical Practice Research Unit, University of Central Lancashire, Preston

Mr Jim Reece
Service User Representative

Dr Karen Roberts,
Nurse Consultant, Dunston Hill Hospital Cottages

Observers

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Department of Health

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), London

Deputy Chair,
Dr David Pencheon,
Director, NHS Sustainable Development Unit, Cambridge

Dr Elizabeth Fellow-Smith,
Medical Director, West London Mental Health Trust, Middlesex

Dr John Jackson,
General Practitioner, Parkway Medical Centre, Newcastle upon Tyne

Professor Mike Kelly,
Director, Centre for Public Health Excellence, NICE, London

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset

Ms Jeanett Martin,
Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust

Dr Julie Mytton,
Locum Consultant in Public Health Medicine, Bristol Primary Care Trust

Miss Nicky Mullany,
Service User Representative

Professor Ian Roberts,
Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Professor Ken Stein,
Senior Clinical Lecturer in Public Health, University of Exeter

Dr Kieran Sweeney,
Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth

Professor Carol Tannahill,
Glasgow Centre for Population Health

Professor Margaret Thorogood,
Professor of Epidemiology, University of Warwick Medical School, Coventry

Observers

Ms Christine McGuire,
Research & Development, Department of Health

Dr Caroline Stone,
Programme Manager, Medical Research Council

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Professor of Social Gerontology & Health Services Research, University of Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer and Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing and Head of Research, The Medical School, University of Birmingham

Professor Barry Cookson, Director, Laboratory of Hospital Infection, Public Health Laboratory Service, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, Institute of Child Health, London

Mr John Dunning, Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Dean of Faculty of Medicine, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts and The London School of Medicine and Dentistry

Mr Leonard R Fenwick, Chief Executive, Freeman Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher, Antenatal Teacher and Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, University of Birmingham

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Professor Fiona Gilbert, Consultant Radiologist and NCRN Member, University of Aberdeen

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, South Tees Hospital NHS Trust

Bec Hanley, Co-director, TwoCan Associates, West Sussex

Dr Maryann L Hardy, Senior Lecturer, University of Bradford

Mrs Sharon Hart, Healthcare Management Consultant, Reading

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Richard Hobbs, Head of Department of Primary Care & General Practice, University of Birmingham

Professor Alan Horwich, Dean and Section Chairman, The Institute of Cancer Research, London

Professor Allen Hutchinson, Director of Public Health and Deputy Dean of ScHARR, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director and Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia

Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry

Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council

Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Children's Health, Lymington

This version of the monograph does not include the appendices. This is to save download time from the HTA website.

The printed version also excludes the appendices.

View/download the appendices

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278