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Appendices

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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

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Appendix 1

Patient information sheets

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A double-blind randomized placebo-controlled trial of topical intranasal steroids in 4- to 11-year-old children with otitis media with effusion (OME) in primary care

Patient Information Sheet

Invitation

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

What is the purpose of the study?

'Glue ear' is a very common condition in children and is particularly common over the winter months. It is a type of catarrh or 'glue' behind the eardrum, which can cause the child to lose some hearing and lead to a variety of different problems. Many children affected by this condition will recover on their own, however some children also have recurrent or persisitent catarrh in their ears and may need further medical treatment and referral. This study aims to see whether a steroid nasal spray given over three months can help such children.

Why has my child been chosen?

Your practice has noted from their records that your child has already had one or more ear infections or ear related problems over the last year that may be associated with glue ear. They are therefore inviting you to an appointment with the practice research nurse for a test that can detect if your child currently has any 'glue' behind the eardrum. This is a simple painless five minute test.

Does my child have to take part?

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

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

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

If you decide to let your child participate in the next part of the study, your child will be allocated at random to either a steroid nasal spray or a nasal spray without medication (called a 'placebo'). This is like tossing a coin to decide which group your child is in. You will not know which spray your child takes, nor will the doctors and nurses in the research team. This is because sometimes if patients and the research team know what medication is being given in a research study it may affect the results.

Your child will take the nasal spray for three months and the practice research nurse will show you how to give it. It is sprayed once a day in each nostril. In the first week of your child starting the spray the practice research nurse will telephone you to make sure that you are not having any problems. Whichever group your child is in they will continue to receive your practice's recommended management for glue ear.

After your child has been taking the spray for a month we will conduct some more ear tests. During the time your child is taking the spray we will ask you to keep a simple diary, filled in once a week for convenience, about the child's symptoms and how they are. We ask you to do this for a total of three months in two diaries. At the end of the three months that your child has been taking the spray for we will again conduct some ear tests. Your child's final visit will be six months after they have finished the nasal spray and again we will conduct some more ear tests. At each visit we will ask you to complete some questionnaires about your child and their health and we will also measure and weigh them. Every time you visit we will also ask you to bring in the bottle of steroid spray so we can check there are no problems with it. The practice nurse will also check your child's notes over two years for consultations related to their ear problems.

What are the possible risks of my child taking part?

The steroid spray has been extensively tested and we are not expecting any side effects. The spray does, however, very occasionally produce short lived nosebleeds, stinging in the nose and discomfort, and more rarely heavier nosebleeds. If there are any side effects that we had not foreseen we would be able to quickly find out what spray your child had been allocated to. Also, as an additional check, we will be monitoring your child's height and weight every time they visit as there is an extremely slight risk of height being affected.

Medical indemnity arrangements

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

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

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

What will happen to the results of the research study?

It is anticipated that the results of the study will be published a year after the conclusion of the research. No child will be identified by name in any publication. The study spray is not currently available for this condition outside of this clinical study nor is it possible to give a repeat prescription whilst in the study.

Who is organising the funding of the research?

The NHS Health Technology Assessment Programme is sponsoring this study. Unfortunately we are unable to reimburse you for your travel expenses.

Contact for further information

The Study Manager, Dr Sarah Benge, Department of Primary Care, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST. Telephone 023 000 0000.

What if I have any other concerns?

If you have any problems, concerns or other questions about this study, you should contact The Study Manager, Dr Sarah Benge, at the above address or discuss them with the research nurse at the practice.

The Metropolitan MREC, one of 13 national research ethics committees, has given its approval for this study.

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

IF YOU DO CHOOSE TO LET YOUR CHILD TAKE PART IN THE STUDY PLEASE KEEP THIS INFORMATION SHEET

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

Version 6, 12/07/05

University of Southampton

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A double-blind randomized placebo-controlled trial of topical intranasal steroids in 4- to 11-year-old children with otitis media with effusion (OME) in primary care

Patient Information Sheet for (6- to 11-year-olds)

You may have got glue ear, which is something a lot of children have.

This means that you could have sticky fluid in your ear that can stop you hearing quiet noises.

Your doctor is helping us with a study to find out better ways of treating glue ear.

If you like you can help us to do this by joining our study.

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

You will have your ears tested by the nurse, then if you have glue ear you will be asked to use a spray in your nose and help the grown-ups keep a diary of how you feel.

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

YOU ARE FREE TO WITHDRAW FROM THE STUDY AT ANY TIME

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

Appendix 2

Initial appointment form

GNOME: initial appointment form

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

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

Postcode: ……..…….. Telephone: ……..……..

Address: ……..

Date of birth: ……

DATE OF APPOINTMENT……

Please remove this top copy with all the patient's details and put the second sheet with the signed consent form, if applicable, into the FREEPOST envelope provided and send it back to Sarah Benge at the University of Southampton

REMEMBER TO COMPLETE THE STUDY ID NUMBER ON THE NEXT SHEET BEFORE YOU START

GNOME: initial appointment form

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

Gender: Male / Female

Age: ……..years …….months

FROM YOUR OBSERVATION REGISTER

Was this child recruited from computer records or referral: computer records / referral

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

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

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

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

a) hearing loss	Yes / No	If yes, how many ……
b) snoring	Yes / No	If yes, how many ……
c) behaviour concerns	Yes / No	If yes, how many ……
d) speech concerns	Yes / No	If yes, how many ……
e) educational concerns	Yes / No	If you, how many ……

EXCLUSION CRITERIA – present?

Does you child have grommets in place? Yes / No

if yes, your child is not eligible because tympanometry, the main measure of the study, is not valid with grommets

Is your child listed for an operation to have grommets put in? Yes / No

if yes, as above

Do you have any concerns about your child's growth? Yes / No

if yes, your child is not eligible, see your health visitor

Is your child hypersensitive to mometasone (Nasonex)? Yes / No

if yes, your child is not eligible as trial medication is mometasone

if none are present, continue

PLEASE TURN OVER

PARENT INFORMED ABOUT TRIAL

☐ Consent obtained immediately ☐ Consent form taken away, to be posted back

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

Remember to chase up any consent forms not returned within 2 weeks of the parents seeing you

Appendix 3

Consent form

University of Southampton

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Primary Medical Care

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Aldermoor Health Centre
Aldermoor Close
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United Kingdom

Tel +44 023 8024 1050
Fax +44 023 8070 1125
Email pmc1@soton.ac.uk

Centre number ……

Study number MREC 03/11/073

Patient ID number …….....

CONSENT FORM

A double-blind randomized placebo-controlled trial of topical intranasal steroids in 4- to 11-year-old children with otitis media with effusion (OME) in primary care

Please initial box

1. I confirm that I have had the study explained to me by the nurse, and had the chance to read the information sheet dated (Version 6, dated 12/7/05, Child's Version 3, dated 26/1/04) and ask questions. ☐

2. I understand that all my child's details will be kept confidential, and their name will not appear on any reports or documents. ☐

3. I understand that taking part in the study will involve further trips for me and my child to the surgery. ☐

4. I understand that if my child participates in the next part of the study I will need to administer the study nasal spray as instructed once a day, and that the total length of treatment is 3 months. ☐

5. I understand that if my child participates in the next part of the study the practice research nurse will need to check my child's medical notes for 12 months before starting the spray and for 9 months thereafter for consultations relating to their ear problems and provide this information to the researchers. I give permission for her to do this. ☐

6. I understand that our participation is voluntary and that we are free to withdraw at any stage without my or my children's medical care or legal rights being affected. ☐

7. I agree to my child participating in this study. ☐

Name of child_____ Date_____Signature_____

Name of parent / guardian_____Date_____Signature_____

Name of nurse_____Date_____Signature_____

3 copies (co-ordinator/patient/practice)

Version 6, 12/07/05

Appendix 4

Beginning of watchful waiting assessment form

GNOME: beginning of watchful waiting form

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

OTOSCOPY *please circle*:

	Clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry (see Appendix 4)	**Wax**	RIGHT	LEFT
	Perforation	RIGHT	LEFT
Exclude child from study ←	**Grommet**	RIGHT	LEFT

TYMPANOMETRY

if **FAIL**, *please circle combination*: B + C2 or B + B

if **PASS**, please tick box indicating patient has been excluded from study and explanation has been given to them as to why ☐

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

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

Please attach print out

Please turn over

OPTIONAL

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

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

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

Version 2, 24/8/04

Appendix 5

End of watchful waiting assessment form

GNOME: end of watchful waiting form

DATE OF APPOINTMENT ……..

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

OTOSCOPY *please circle*:

	Clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry (see Appendix 4)	**Wax**	RIGHT	LEFT
	Perforation	RIGHT	LEFT
Exclude child from study ←	**Grommet**	RIGHT	LEFT

TYMPANOMETRY

if **FAIL**, *please circle combination*: B + C2 or B + B

if **PASS**, please tick box indicating patient has been excluded from study and explanation has been given to them as to why ☐

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

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

Please attach print out

Please turn over

If FAIL recorded from tympanometry

CHECK ADMISSION CRITERIA MET ☐ Yes ☐ No

If yes, continue

CHECK EXCLUSION CRITERIA

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

If yes, your child is not eligible because tympanometry, the main measure of the study, is not valid with grommets

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

If yes, as above

Do you have any concerns about your child's growth? ☐ Yes ☐ No

If yes, your child is not eligible, see your health visitor

Is your child hypersensitive to mometasone (Nasonex)? ☐ Yes ☐ No

If yes, your child is not eligible as trial medication is mometasone

Has your child had systemic steroids in the previous 3 months or do they have poorly controlled asthma? ☐ Yes ☐ No

If yes, your child is not eligible because we don't want to exceed the steroid dose

Has your child had recent epistaxis in the last month? ☐ Yes ☐ No

If yes, your child is not eligible as the spray could make their nose bleed

If none are present, continue

PARENT INFORMED ABOUT SECOND PART OF TRIAL

Give second letter to parent and go through the consent form that they signed at the beginning.

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

……

……

……

OPTIONAL

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

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

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

Version 2, 24/8/04

Appendix 6

Baseline assessment forms

GNOME: baseline measures form

DATE OF APPOINTMENT ……..

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

SPRAY NUMBER GIVEN: ……

SWEEP PURE TONE AUDIOMETRY (BASELINE)

Performed at **25dB** in a ***quiet room***

✓ = pass **× = fail**

	0.5 kHz	**1 kHz**	**2 kHz**	**3kHz**	**4kHz**
Right ear					
Left ear					

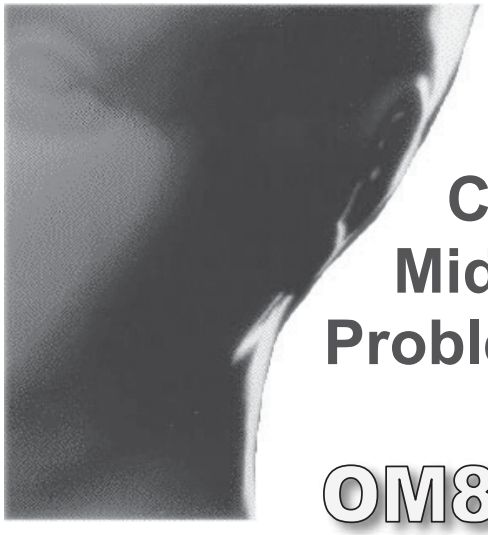
Comment: co-operative ☐ not co-operative ☐

OPTIONAL

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

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

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



Children's Middle Ear Problems

OM8-30

Parent* questionnaire

Study number

Baseline measures

**For parents or other regular caregivers*

Notes to parents on questionnaire completion

- For all questions, please tick **ONE** box opposite the description that *best fits* your child (even if you feel the description may not be absolutely accurate).

- Please be aware of the time period that the question is referring to, and answer for this time period – usually 3 months.

Thank you for completing this questionnaire;
all information given by you will be treated in confidence

OM8-30: Questionnaire

Section A: Global health

This question refers to the last 3 months

1. Taking everything into account, how would you say that your child's health has been?	
Very good	☐
Good	☐
Fair	☐
Poor	☐

Section B: Respiratory symptoms

2. How often does he/she get colds?	
Once a week	☐
Once every 2–3 weeks	☐
Once every 1–3 months	☐
Once every 4–6 months	☐
Less often	☐
Never	☐
Not sure	☐

The remaining questions in this section refer to the last 3 months

3. How many times has he/she had a cough, cold or sore throat?	
Not at all	☐
Once	☐
2–3 times	☐
4–5 times	☐
6 or more times	☐

4. Has he/she breathed through his/her mouth?	
Never	☐
Rarely	☐
Often	☐
Always	☐
Only when he/she has a cold	☐
Not sure	☐
5. Has he/she sounded as if he/she has a blocked nose?	
Never	☐
Rarely	☐
Often	☐
Always	☐
Only when he/she has a cold	☐
Not sure	☐
6. Has he/she* usually *had a runny nose?	
No	☐
Yes – clear	☐
Yes – purulent (yellowish or greenish)	☐
Only when he/she has a cold	☐
Not sure	☐
7. Has he/she snored or breathed heavily at night?	
Never	☐
Rarely	☐
Often	☐
Always	☐
Only when he/she has a cold	☐
Not sure	☐

Section C: Ear problems

All questions in this section refer to the last 3 months

8. How many times has he/she had trouble with his/her ears?	
Not at all	☐
Once	☐
2–3 times	☐
4–5 times	☐
6 or more times	☐
9. How many ear infections has he/she had? **(i.e. severe pain in his/her ear, possibly with a temperature)**	
0	☐
1	☐
2–3	☐
4 or more	☐
Not sure	☐
10. How many times has he/she had an earache?	
0	☐
1	☐
2–3	☐
4 or more	☐
Not sure	☐

Section D: Reported hearing difficulties

All questions in this section refer to the last 3 months

11. How would you describe your child's hearing?	
Normal	☐
Slightly below normal	☐
Poor	☐
Very poor	☐
Not sure	☐
12. Has he/she misheard words when not looking at you?	
No	☐
Rarely	☐
Often	☐
Always	☐
Not sure	☐
13. Has he/she had difficulty hearing when with a group of people?	
No	☐
Rarely	☐
Often	☐
Always	☐
Not sure	☐
14. Has he/she asked for things to be repeated?	
No	☐
Rarely	☐
Often	☐
Always	☐
Not sure	☐

Section E: Behaviour

All questions in this section refer to the last 3 months

15. Sitting still (e.g. at meal time, story time or at other times) he/she…	
Is very active and does not sit still when necessary	☐
Can usually sit still when necessary	☐
Can sit still for a long period	☐
Is not active enough	☐
16. How long can he/she concentrate on a game or task you have given him/her to do?	
Up to 2 minutes	☐
Up to 5 minutes	☐
5–10 minutes	☐
10–15 minutes	☐
More than 15 minutes	☐
17. How often does he/she seek your attention unnecessarily? **(e.g. asking for help for a task he/she can do themselves, demanding to be carried, demanding you to play with him/her, following you around)**	
Less than once a month	☐
Once a month	☐
Once a week	☐
Once a day	☐
Two or three times a day	☐
18. How often does he/she whine or moan with little reason?	
Less than once a month	☐
Once a month	☐
Once a week	☐
Once a day	☐
Two or three times a day	☐

19. How often is he/she unhappy for no apparent reason?	
Less than once a month	☐
Once a month	☐
Once a week	☐
Once a day	☐
Two or three times a day	☐
20. When you take him/her out somewhere, does he/she do what you ask?	
Never	☐
Sometimes	☐
Often	☐
Always	☐

Section F: Speech and language

All questions in this section refer to the last 3 months

21. Has he/she mispronounced the beginnings or ends of words?	
No	☐
Rarely	☐
Often	☐
Always	☐
Not sure	☐
22. Has his/her speech been behind (less developed than) that of children of a similar age?	
No	☐
A little	☐
Moderately	☐
A lot	☐
Not sure	☐
23. When trying to tell you something, does he/she have poor articulation? **(e.g. unclear speech, missing out sounds, or producing the wrong sound)**	
Yes	☐
No	☐

Section G: Sleep patterns

All questions in this section refer to the last 3 months

24. Do you think that the ear, nose or throat problems affect his/her sleep?	
Nearly always	☐
Sometimes	☐
Hardly ever	☐
25a. Would you say that your child is tired or listless during the day?	
Almost always	☐
Sometimes	☐
Never	☐
25b. If he/she is tired or listless during the day, do you think this happens at the same time as his/her ear, nose or throat condition?	
Almost always	☐
Sometimes	☐
Never	☐
Not applicable	☐

Section H: School prospects

This question refers to the last 3 months

26. Have you worried that your child's ear, nose or throat problem might slow down his/her progress at school?	
Often worried	☐
Sometimes worried	☐
Never worried	☐

Section I: Parent quality of life

All questions in this section refer to the last 3 months

27. Have your child's ear, nose or throat problems meant that you often feel tired?	
Yes	☐
No	☐
28. Has your child needed more attention than other children?	
Yes	☐
No	☐
29. Has your child been very demanding?	
Yes	☐
No	☐
30. Has it taken a lot of energy to cope?	
Yes	☐
No	☐
31. Would you agree that people wouldn't realise the effort involved until they had a child with ear or hearing problems?	
Yes	☐
No	☐

GNOME: Costs to parents 1

To be done when taking baseline measures

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

1. Self-medication use for ear problems

Over the **past 12 months** have you self-treated your child (without coming to surgery) for an ear problem?

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

If YES, How many occasions? ☐ 0–1 ☐ 1–2 ☐ 2–4 ☐ More than 4

b) Using a nose spray? ☐ Yes ☐ No

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

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

If YES, How many occasions? ☐ 0–1 ☐ 1–2 ☐ 2–4 ☐ More than 4

2. Activities

Has your child's teacher been concerned about ….

a) Your child not paying attention in class ☐ Yes ☐ No

If YES, how much
- ☐ Not at all
- ☐ Not very much
- ☐ A little
- ☐ Fairly concerned
- ☐ Very concerned

b) Your child's hearing in class ☐ Yes ☐ No

If YES, how much
- ☐ Not at all
- ☐ Not very much
- ☐ A little
- ☐ Fairly concerned
- ☐ Very concerned

Please turn over

c) Your child being dreamy in class ☐ Yes ☐ No

If YES, how much
☐ Not at all
☐ Not very much
☐ A little
☐ Fairly concerned
☐ Very concerned

d) Does your child enjoy swimming ☐ Yes ☐ No

If YES, how concerned are you that your child's ear problems/hearing have interfered with their swimming activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

e) Does your child enjoy music Yes ☐ No ☐

If YES, how concerned are you that your child's ear problems/hearing have interfered with their music activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

f) Does your child enjoy sports Yes ☐ No ☐

If YES, how concerned are you that your child's ear problems/hearing have interfered with their sports activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

g) Does your child enjoy dancing ☐ Yes ☐ No

If YES, how concerned are you that your child's ear problems/hearing have interfered with their dancing activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

h) How much time do you think your child has lost from school, nursery or playgroup over the past year because of ear problems

☐ Less than 1 week ☐1 week ☐ 2 weeks ☐ 3 weeks

☐ 4 weeks ☐5 weeks ☐ 6 weeks ☐ More than 6 weeks

i) Does your child suffer from:

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

3. Occupation

a) How do you describe your present occupation? ……..

Is this part time? ☐ Yes ☐ No ☐ Not applicable

b) If you have a partner living in the household, how would you describe their present occupation?

……

Is this part time? ☐ Yes ☐ No ☐ Not applicable

c) How many occasions have you or a guardian of the child been unable to work or do your normal daily activities because of your child's ear problems over the last year?

☐ 0	☐1	☐2	☐ 3	☐ 4	☐ 5	☐ 6
☐ 7	☐ 8	☐9	☐10	☐11	☐ 12	☐More than 12

version 2, 24/8/04

GNOME: adherence questionnaire

To be done 7 days after BASELINE MEASURES taken

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

SPRAY NUMBER GIVEN: ……

'Hello my name is …….. the research nurse working on the research trial your child has just entered. Would it be OK to ask a few questions about your use of the nasal spray – it should only take a few minutes. If it's inconvenient at the moment I can call back at a more convenient time. The information you give is entirely confidential.

Just to check……..'

1. Can you tell me the name of the nasal spray you were given as part of our study?

……

2. What is the reason for using the nasal spray?

……

3. Does your child still have the condition or problem that the nasal spray was given for?

……

If yes, the condition / problem has improved ☐ Yes ☐ No
the condition / problem has not changed ☐ Yes ☐ No
the condition / problem has got worse ☐ Yes ☐ No

4. Has your child started taking the nasal spray? ☐ Yes ☐ No

5. How many days has your child been taking it?.....

6. How many times a day is your child taking it?.....

Please turn over

7. How many squirts do you use into each nostril each time?.....

8. How many times has your child missed taking the nasal spray?.....

9. How well do you think this spray is working for your child?

☐ Very well ☐ OK ☐ Not well

10. Have you any concerns or experienced any problems about your child taking this nasal spray?

a) The nasal spray has not worked / does not work	☐ Yes	☐ No
b) It gives my child unwanted effects (side-effects)	☐ Yes	☐ No
c) It is difficult to give to my child	☐ Yes	☐ No
d) I worry about the long term use of this spray	☐ Yes	☐ No
e) I am concerned this spray may be harmful	☐ Yes	☐ No

f) Any other problems……

……

11. Would you like more information about the nasal spray or study in general? ☐ Yes ☐ No

If yes, what?.....

12. Have you experienced any difficulties with recording the symptom diary? ☐ Yes ☐ No

If yes, what?.....

13. Do you think your child is taking the active nose spray? ☐ Yes ☐ No ☐ Don't know

14. If your child had not taken the spray would you have told me? Yes ☐ No ☐

FINALLY – do you have any comments you would like to add?……

……

……

THANK YOU FOR YOUR TIME

and just to confirm your next appointment with me is on……..

version 2, 24/8/04

GNOME: Health Economics Evaluation Form 1

To be done at time of taking BASELINE MEASURES by computer search

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

In the previous 15 months

1. All appointments for OM or OME (ear problems)

a) List the dates of appointments with GP: ……

b) List the dates of appointments with nurse: ……...

c) List the dates of appointments with health visitor: ……..……..

d) List the dates of home visits: ……..……..

e) List the dates of telephone consultations: with GP ...……

with nurse ……...

f) List the dates of out of hours consultations: ……...……

2. Referral for OM or OME (ear problems)

a) Date ……

b) Main reason ……..……...…

……

c) To where? ☐ ENT ☐ Audiology ☐ Other

please state ……...……

3. Hospitalisation

a) Grommets / t-tubes / ventilation tubes: Yes / No Date(s) ……..

b) Adenoidectomy: planned Yes / No Date ……

done Yes / No Date ……

Please turn over

4. Treatment courses for OM or OME (ear problems)

a) Antibiotics:

Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……

b) Autoinflation Yes / No Date …….

c) Decongestants and antihistamines:

Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……

d) Analgesics:

Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……
Date …….. name …….. dose …….. days ……

5. Investigations for OM or OME (hearing problems)

e.g. blood tests / X-rays,

please give dates : ……

……

……

……

version 1, 1/7/03

Appendix 7

One-month assessment forms

GNOME: 1 month measures form

DATE OF APPOINTMENT ……..

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

SPRAY NUMBER GIVEN: ……

VISIT 1 SPRAY collected ☐ Yes ☐ No **4 week diary collected** ☐ Yes ☐ No

NASAL SPRAY ADHERENCE

Did your child take the spray ….

☐ Not at all ☐ Some of the time ☐ Most of the time ☐ All of the time

CHECK REFERRAL STATUS

Has your child been referred to an ENT surgeon ☐ Yes ☐ No

If yes, has the surgeon recommended surgery ☐ Yes ☐ No

If yes, do you have an appointment yet ☐ Yes ☐ No

When ……

CHECK ADVERSE EVENTS / SIDE EFFECTS

Stinging in the nose	☐ Yes	☐ No
Nosebleed	☐ Yes	☐ No
Dryness and irritation at back of throat	☐ Yes	☐ No
Diarrhoea	☐ Yes	☐ No
Cough	☐ Yes	☐ No

If none, continue

If the patient has had a side effect that has settled they can continue with the study

If patient and/or parents are concerned about the side effects or they are severe they should be referred to the GP

Please turn over

OTOSCOPY *please circle*:

	Clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry (see Appendix 4)	**Wax**	RIGHT	LEFT
	Perforation	RIGHT	LEFT
Child continues with study ←	**Grommet**	RIGHT	LEFT

TYMPANOMETRY

if **FAIL**, *please circle combination*: B + C2 or B + B

if **PASS**, *please circle combination*: A + A A + B A + C1 A + C2
C1 + B C1 + C2 C1 + C1 C2 + C2

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

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

Please attach print out

SWEEP PURE TONE AUDIOMETRY (1 MONTH)

Performed at **25dB** in a ***quiet room***

✓ = pass × = fail

	0.5 kHz	1 kHz	2 kHz	3 kHz	4 kHz
Right ear					
Left ear					

Comment: co-operative ☐ not co-operative ☐

OPTIONAL

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

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

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

version 2, 24/8/04

GNOME: adherence questionnaire

To be done 7 days after 1 month MEASURES taken

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

SPRAY NUMBER GIVEN: ……

'Hello my name is …….. the research nurse working on the research trial your child has just entered. Would it be OK to ask a few questions about your use of the nasal spray – it should only take a few minutes. If it's inconvenient at the moment I can call back at a more convenient time. The information you give is entirely confidential.

Just to check……'

1. Can you tell me the name of the nasal spray you were given as part of our study?

……

2. What is the reason for using the nasal spray?

……

3. Does your child still have the condition or problem that the nasal spray was given for?

……

If yes, the condition / problem has improved ☐ Yes ☐ No
the condition / problem has not changed ☐ Yes ☐ No
the condition / problem has got worse ☐ Yes ☐ No

4. Has your child started taking the nasal spray? ☐ Yes ☐ No

5. How many days has your child been taking it?.....

6. How many times a day is your child taking it?.....

Please turn over

7. How many squirts do you use into each nostril each time?.....

8. How many times has your child missed taking the nasal spray?.....

9. How well do you think this spray is working for your child?

☐ Very well ☐ OK ☐ Not well

10. Have you any concerns or experienced any problems about your child taking this nasal spray?

a) The nasal spray has not worked / does not work ☐ Yes ☐ No
b) It gives my child unwanted effects (side effects) ☐ Yes ☐ No
c) It is difficult to give to my child ☐ Yes ☐ No
d) I worry about the long term use of this spray ☐ Yes ☐ No
e) I am concerned this spray may be harmful ☐ Yes ☐ No
f) Any other problems……
……

11. Would you like more information about the nasal spray or study in general? ☐ Yes ☐ No
If yes, what?.....

12. Have you experienced any difficulties with recording the symptom diary? ☐ Yes ☐ No
If yes, what?.....

13. Do you think your child is taking the active nose spray? ☐ Yes ☐ No ☐ Don't know

14. If your child had not taken the spray would you have told me? Yes ☐ No ☐

FINALLY – do you have any comments you would like to add?……
……
……

THANK YOU FOR YOUR TIME

and just to confirm your next appointment with me is on……..

Appendix 8

Three-month assessment form

GNOME: 3 month measures form

DATE OF APPOINTMENT ……..

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

SPRAY NUMBER: ……

VISIT 2 SPRAY collected ☐ Yes ☐ No **8 week diary collected** ☐ Yes ☐ No

NASAL SPRAY ADHERENCE

Did your child take the spray ….

☐ Not at all ☐ Some of the time ☐ Most of the time ☐ All of the time

CHECK REFERRAL STATUS

Has your child been referred to an ENT surgeon ☐ Yes ☐ No

If yes, has the surgeon recommended surgery ☐ Yes ☐ No

If yes, do you have an appointment yet ☐ Yes ☐ No

When ……

CHECK ADVERSE EVENTS / SIDE EFFECTS

Stinging in the nose	☐ Yes	☐ No
Nosebleed	☐ Yes	☐ No
Dryness and irritation at back of throat	☐ Yes	☐ No
Diarrhoea	☐ Yes	☐ No
Cough	☐ Yes	☐ No

If patient and/or parents are concerned about the side effects or they are severe they should be referred to the GP

Please turn over

OTOSCOPY *please circle*:

	Clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry (see Appendix 4)	**Wax**	RIGHT	LEFT
	Perforation	RIGHT	LEFT
Child continues with study ←	**Grommet**	RIGHT	LEFT

TYMPANOMETRY

if **FAIL**, *please circle combination*: B + C2 or B + B

if **PASS**, *please circle combination*: A + A A + B A + C1 A + C2
C1 + B C1 + C2 C1 + C1 C2 + C2

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

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

Please attach print out

SWEEP PURE TONE AUDIOMETRY (3 MONTHS)

Performed at **25dB** in a ***quiet room***

✓ = pass **× = fail**

	0.5 kHz	**1 kHz**	**2 kHz**	**3 kHz**	**4 kHz**
Right ear					
Left ear					

Comment: co-operative ☐ not co-operative ☐

OPTIONAL

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

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

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

Appendix 9

Nine-month assessment forms

GNOME: 9 month measures form

DATE OF APPOINTMENT ……..

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

OTOSCOPY *please circle*:

	Clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry (see Appendix 4)	**Wax**	RIGHT	LEFT
	Perforation	RIGHT	LEFT
Child continues with study ←	**Grommet**	RIGHT	LEFT

TYMPANOMETRY

if **FAIL**, *please circle combination*: B + C2 or B + B

if **PASS**, please *circle combination*:

A + A	A + B	A + C1	A + C2
C1 + B	C1 + C2	C1 + C1	C2 + C2

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

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

Please attach print out

Please turn over

SWEEP PURE TONE AUDIOMETRY (9 months)

Performed at **25dB** in a ***quiet room***

✓ = pass **× = fail**

	0.5 kHz	**1 kHz**	**2 kHz**	**3 kHz**	**4 kHz**
Right ear					
Left ear					

Comment: co-operative ☐ not co-operative ☐

OPTIONAL

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

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

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

version 2, 24/8/04

GNOME: Costs to parents 2

To be done at time of SIXTH NURSE ASSESSMENT – at time of 9 month measures

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

1. Self-medication use for ear problems

Over the **past 12 months** have you self-treated your child (without coming to surgery) for an ear problem?

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

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

b) Using a nose spray? ☐ Yes ☐ No

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

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

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

2. Activities

Has your child's teacher been concerned about

a) Your child not paying attention in class ☐ Yes ☐ No

If YES, how much
- ☐ Not at all
- ☐ Not very much
- ☐ A little
- ☐ Fairly concerned
- ☐ Very concerned

b) Your child's hearing in class ☐ Yes ☐ No

If YES, how much
- ☐ Not at all
- ☐ Not very much
- ☐ A little
- ☐ Fairly concerned
- ☐ Very concerned

Please turn over

c) Your child being dreamy in class ☐ Yes ☐ No

If YES, how much
☐ Not at all
☐ Not very much
☐ A little
☐ Fairly concerned
☐ Very concerned

d) Does your child enjoy swimming ☐ Yes ☐ No

If YES, how concerned are you that your child's ear problems/hearing have interfered with their swimming activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

e) Does your child enjoy music Yes ☐ No ☐

If YES, how concerned are you that your child's ear problems/hearing have interfered with their music activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

f) Does your child enjoy sports Yes ☐ No ☐

If YES, how concerned are you that your child's ear problems/hearing have interfered with their sports activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

g) Does your child enjoy dancing ☐ Yes ☐ No

If YES, how concerned are you that your child's ear problems/hearing have interfered with their dancing activities?

☐ Not at all ☐ Not very much ☐ A little ☐ Fairly concerned ☐ Very concerned

h) How much time do you think your child has lost from school, nursery or playgroup over the past year because of ear problems?

☐ Less than 1 week ☐ 1 week ☐ 2 weeks ☐ 3 weeks

☐ 4 weeks ☐ 5 weeks ☐ 6 weeks ☐ More than 6 weeks

3. Occupation

a) How do you describe your present occupation? ……..

Is this part time? ☐ Yes ☐ No ☐ Not applicable

b) If you have a partner living in the household, how would you describe their present occupation?

……

Is this part time? ☐ Yes ☐ No ☐ Not applicable

c) How many occasions have you or a guardian of the child been unable to work or do your normal daily activities because of your child's ear problems over the last year?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ More than 12

4. Adverse events

Over the **past 12 months** has your child had the following:

vertigo (spinning or dizzy episodes) Yes ☐ No ☐

GNOME: Health Economics Evaluation Form 2

To be done at time of SIXTH NURSE ASSESSMENT – 9 months into trial

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

In the previous 9 months

1. All appointments for OM or OME (ear problems)

a) List the dates of appointments with GP: ……

b) List the dates of appointments with nurse: ……...

c) List the dates of appointments with health visitor: ……..……..

d) List the dates of home visits: ……..……..

e) List the dates of telephone consultations: with GP ...……

with nurse ……...

f) List the dates of out of hours consultations: ……...……

2. Referral for OM or OME (ear problems)

a) Date ……

b) Main reason ……..……...…

……

c) To where? ☐ ENT ☐ Audiology ☐ Other

please state ……...……

3. Hospitalisation

a) Grommets / t-tubes / ventilation tubes: Yes / No Date(s) ……..

b) Adenoidectomy: planned Yes / No Date ……

done Yes / No Date ……...

Please turn over

4. Treatment Courses for OM or OME (ear problems)

a) Antibiotics:

Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..

b) Autoinflation Yes / No Date …….

c) Decongestants and antihistamines:

Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..

d) Analgesics:

Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..

5. Investigations for OM or OME (hearing problems)

e.g. blood tests / X-rays,

please give dates : …….

…….

…….

…….

GNOME: EXIT INTERVIEW

Study ID number:							

This is a short semi-structured interview with the parent / guardian and child covering any comments from taking part, any medication or treatment preferences and brief specific guidelines as requested.

Ask them (child and parent / guardian) for their comments on taking part in the trial (good things, bad things, etc.)

.....

.....

.....

.....

.....

.....

.....

.....

Ask them if they had any treatment preferences throughout the trial, e.g. the trial spray, any antibiotics, nasal drops they were prescribed

.....

.....

.....

Ask them what they will do now with regard to their child's condition

.....

.....

.....

.....

.....

PLEASE GIVE THEM A LEAFLET

AND OUR THANKS version 1 dated 14 Feb 2006

Appendix 10

Diary

Study number | | | | | | | |

WEEK 1

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

0	1	2	3	4	5	6	7

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

0	1	2	3	4	5	6	7

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

0	1	2	3	4	5	6	7

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

0	1	2	3	4	5	6	7

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

0	1	2	3	4	5	6	7

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

0	1	2	3	4	5	6	7

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

0 = Not present at all 1 = Very little problem 2 = Slight problem 3= Moderately bad 4 = Bad 5 = Very bad 6 = As bad as it could be

Has your child.....	Yes	No	How bad at its worst
Been clumsy / off balance			
Been unwell / had a temperature			
Had a runny nose			
Had a blocked nose / been snoring			
Had stinging / discomfort in their nose and sneezing			
Had any nosebleeds			
Had any dryness in nose or throat			

Appendix 11
Early protocols

First version

The University of Southampton

Title

A double-blind randomised placebo-controlled trial of topical intranasal steroids in 3- to 11-year-old children with persistent bilateral OME in primary care.

How has the project changed since the outline proposal was submitted?

The project has been critically developed from outline to a full submission by incorporating the most recent research findings, both published and unpublished. In particular we have taken heed of the reviewers' general feedback to address the brief's requirements in relation to cost-effectiveness, by developing the overall trial methodology and analyses towards longer term outcomes important to the NHS.

Planned investigation

Research objectives

1. To assess the effectiveness, and cost-effectiveness, of topical intranasal steroids over 1 year (in total) in a pragmatic clinical trial.
2. 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.

Introduction

Otitis media with effusion is an almost universal condition of childhood, and in its chronic and recurrent forms is a source of substantial NHS costs, with over £200M per year spent on related otitis media prescribing, and an additional £30M in costs to the NHS for grommets, the operation used to treat the more persistent and/or severe cases. The majority of children are referred from primary care, but confusions over treatment and uncertain diagnosis here 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 to curb the processes of referral. Now, with the about to be published findings of substantial benefit from surgery from the trial of alternative regimens in glue ear treatment (TARGET), albeit in selected cases, rates look set to rise again, unless primary care management becomes more effective for this problem. Currently, however, there are no effective treatments available in primary care, thus the requirement to develop them is now urgent.

Existing research

Otitis media with effusion treatments have been, and are being, extensively reviewed (*BMJ Clinical Evidence*, Cochrane reviews on; steroids, grommets, antibiotics) because OME is a source of substantial morbidity in children, and considerable costs to the NHS.[1–6] It leads to hearing loss, delays in language and behaviour development, and is the commonest reason for surgery in children.[7,8] While the TARGET trial is currently clarifying the role for surgery in restricted and persistent cases, there is, and is likely to remain, a need for medical treatments for temporising management, or as an alternative or adjunct to surgery.[9,10] The aims of interventions should be to secure improvement in hearing and well-being of affected children and to minimise poor behavioural, speech and educational outcomes.[1] As OME is a highly recurrent condition with a mean duration of 6–10 weeks, outcomes need to be evaluated over a reasonable 6-month to 1-year period.[11–13] Few quality studies of any treatment have followed up children beyond 3 months, and very few address more child-centred outcomes and QoL issues.

The use of a well-validated QoL measure is essential in addition to tympanometry and audiometry as there may not be a close relationship between these observed outcomes and the reported QoL.

Secondary research has allowed a re-evaluation of the benefits of antibiotics in OME showing 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 2002). Furthermore, prescribing antibiotics encourages belief in them, re-attendance, and increasing antibiotic resistance in strains of *Streptococcus pneumoniae*.[14–17] Side-effects, costs and

substantial compliance issues for longer three or four times a day courses render them now untenable as a treatment for OME.

The use of *systemic* steroids has been recommended in combination with antibiotics as cost-effective in OME, but this is based on a low quality meta-analysis, which included trials rejected by the Cochrane review.[18] 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.[19] These concerns in the absence of better evidence of sustained and worthwhile effect from the small and heterogeneous trials included in Cochrane effectively preclude their use for a mild condition with an episodic natural history such as OME.[20–27] Thus on a priori grounds, *topical* intranasal steroids are a logical treatment for evaluation in OME. Our group has been interested in this possibility since the early 1990s, following on from Berman's work. There are several theoretical bases for topical intranasal treatment, and these include phospho-lipid membrane and decongestant/anti-inflammatory effects to the nasal mucosa.[28,29]

This therapeutic approach has now been identified as of value by the Cochrane review of topical intranasal steroids in OME (date of last search January 2002). The review, however, does not recommend use of topical nasal steroids, because of insufficient high quality evidence, although the favourable trial by Tracy and Demain[30] was highly rated on methodological criteria.[31] This trial included only 61 children, and was set in a military airbase in the USA, possibly 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 referred 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 can 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, taking into account the relatively slow resolution of OME, should preferably be given for several months.

Serious side-effects for inhaled topical steroids are rare, but there are concerns that growth may be affected.[32] This makes it imperative that a topical steroid is chosen with minimal systemic effects.

We are aware of an unpublished double-blind RCT of Flixonase in children aged 4 years and over from a tertiary care setting.[33] The trial has good adherence over 2 years and appears effective in preventing recurrences of OME in a severe case-mix group. There are, however, no RCTs from a UK primary care population, hence treatment effects are unknown in the real setting where watchful waiting occurs, and thus there is no evidence base to guide the optimal management of the bulk of significant but proportionately milder cases (differences of case-mix limits generalisability to primary care, from secondary care trials). Any trial on cost-effectiveness needs to consider which groups are most likely to benefit. Thus we aim 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 watchful waiting) and in the group most likely to be referred (i.e. 3 years and over). Medical treatment in these groups is most likely to impact on NHS resource use. To increase the robustness and stringency of the trial we will use microtympanometry. We will be evaluating such improved systems of waiting and treatment for affected children and their families at a time when demand for surgery is likely to be rising again as a result of the TARGET findings and policy expectations of the NHS (changing patterns and an overall increase in referrals). Thus, an NHS trial should not only document referral rates in long-term follow-up but also assess the potential impact of different referral rates and thresholds on management and surgery using modelling techniques.

In summary, we think this review of the evidence makes it clear that there is need for a trial of nasal steroids in OME that has the following features:

- children with persistent bilateral effusion
- follow-up in the medium term (more than 6 months)
- addresses validated child-centred outcomes (e.g. QoL issues) in addition to audiometry and tympanometry
- use a treatment with low systemic absorption, for at least 3 months during the winter months

- assess benefit in those children who are most likely to be referred (i.e. 3 years and over)
- assesses health service resource use and models the impact of likely changes in referral pattern.

Research methods

A double-blind randomised placebo-controlled trial. The main analysis will be on an ITT basis.

Setting

The proper setting for the trial is primary care, and so to achieve generalisability we aim to recruit from 60 practices throughout the UK. We plan to utilise the MRC GPRF to ensure high quality standards in recruitment and follow-up.

Target population

Children aged between 3 and 11 years will be identified from participating practices, through new and follow-up doctor/health-visitor or nurse consultations for current suspected OME, and from regular audit of the notes. The proposal is to identify children who have persistent bilateral effusion, i.e. with abnormal tympanometry in both ears which has persisted for 3 months. Children will be identified for screening with tympanometry in the following ways:

- A monthly search of notes will be made during the autumn and winter months (September through to February) for children presenting to the GP or nurse and a diagnosis of OME is made.
- Nurses will also identify two broad types of at risk children. They will use established search methods applied to the notes in September and October of each study recruitment year. Type 1 children will be identified by typical OME histories from the notes, i.e. those with identified hearing loss, snoring, behaviour, speech and 'educational concerns' consultations. Three or more such ear *problem* consultations identified over the preceding 12 months will constitute sufficient risk for screening.[34]
- Type 2 children are otitis-prone children (AOM) who will be similarly identified but on the reported frequency of all otitis media episodes. Otitis-prone children are well recognised at being at high risk of developing OME.[35] There is no agreed definition of otitis proneness: we have chosen three or more otitis media labelled episodes (separated by 2 weeks from each other) over the 12 preceding months as a pragmatic definition of proneness because (1) we will be recruiting going into winter, so need to look at the previous winter, (2) we want to include most at risk children as we will be screening not treating and (3) this is still a small minority of children with otitis media and thus will not have major workload implications.[36]

We will proceed to carry out monthly audit and assessment for the subsequent winter months (up to February) to pick up any new episodes or missed cases. All children so identified (with the bulk at the beginning of the autumn term) will require tympanometric confirmation of bilateral OME on two occasions 3 months apart using the modified Jerger classification (B + B, B + C2).[37,38]

Randomisation

We have discussed concealment issues with the manufacturers (Schering-Plough). The company will use computer-generated random number lists using formula-generated sequences from pre-specified software input, in order to sequence randomised treatment blocks of four (two with active treatment, two with placebo). These will be distributed to trial personnel who are blind to the medication, supplied as estimated and required. We will ensure that double-blinding is total and effective so that the research nurse can pick the next trial pack from the tray and log that they have done so using a unique medication ID and a unique child ID number. The company will keep the randomisation code at a distant site, and so does not propose the more logistically complex and costly telephone randomisation method as offering any advantages.[39,40]

Health technologies being assessed

Patients meeting entry criteria and giving full informed consent will be randomised to receive placebo or topical intranasal steroids given once a day for 3 months. We will use mometasone 50 µg in each nostril (total daily dose 100 µg) because of its low systemic absorption and specified safety profile.[41–43] The trial will be organised as an adjunct or extra to usual treatment of such children by the practice.

Protection against other sources of bias

Recruitment bias will be assessed by asking GPs and nurses to keep a simple tally and log of all patients consulting with the condition and to tick boxes for the five categories of loss to follow-up in randomised trials: refusal of randomisation, rejection of treatment path, logistical reasons (e.g. intended house moving), other reasons and DNAs. The reason for not recruiting will be recorded in

the log book. We will include ENT referrals over this period as an important reason for non-entry. Brief clinical characteristics of those not entered will be documented and their postcode will provide gross information on material deprivation. We will use a post-study questionnaire to find out why the lowest recruiting GPs did not recruit.[44]

We will ensure that treatment and placebo taste as similar as possible, and will evaluate concealment by testing placebo/treatment recognition by asking parents by telephone at 7 days, before any treatment effects would be expected. We will also ask them at the end of the trial to estimate placebo effects. The investigators, GPs and nurses will be kept blind to the allocation throughout the duration of the trial except in the event of adverse reactions (see Ethical arrangements). We will test randomisation by assessing the distributions of important prognostic factors by group.

We will quantify response bias by comparing the same important clinical predictors in those completing the study at 9 months and those lost to follow-up (for potential effect modifiers see Subgroup analyses). We estimate less than 5% loss to follow-up at 3 months and less than 15% at 9 months because we envisage parents/children will be motivated and we are using a reliable network.[45]

Interventions
Topical intranasal steroids: mometasone furoate 50 µg in each nostril once daily for 3 months versus placebo in each nostril once daily for 3 months. The appropriate method of using the spray with the chin-up will be demonstrated and assessed so that the maximal dose to the posterior nasal space is achieved. This is 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. We will supplement this with a succinct illustrated patient information sheet on aims, use, safety and side-effects. We will evaluate compliance by measuring before and after individual bottle-weights. We will use non-directive questioning, e.g. 'Have you any concerns or experienced any problems with this medication?', at the follow-up nurse clinic and telephone interviews, based on a modified brief adherence questionnaire.[46] In our considerations of duration and compliance we note that two trials have achieved effective compliance for 3 months and 2 years respectively using topical steroids, albeit from secondary care.[30,33] A shorter course, i.e. 2 months, would have less impact on recurrence, whereas the timing of the end of watchful waiting for January/early February will mean that a subsequent 3-month course has the potential in terms of cost-efficiency both to prevent some early recurrences (secondary to seasonal viral infections and atopy), and also to better cover the natural incidence peak in the spring term.[12] Any longer than 3 months would introduce greater complexities in relation to administration, would increase side-effects, might delay important management decisions in relation to children identified 6 months earlier and does not take account of the strong seasonal resolutional effects around this time.[9,12] We are using a once daily dosing schedule to encourage compliance.

Inclusion criteria
Children aged between 3 and 11 years old identified by participating practices and have bilateral OME on tympanometry on two occasions 3 months apart; using the modified Jerger classification (B + B, B + C2).[37,38,47] A B tympanogram has a positive predictive value of 84%, and a C2 of 54%.[48]

Thus children who have persistent effusions after a 3-month period of watchful waiting, who do not meet exclusion criteria and whose parents consent will be entered. The treatment may feasibly be taken by children as young as 3 years. Although children younger than 3 may benefit, delivery of nasal steroids is more problematic, and cost-effectiveness needs to be demonstrated in the older group first, which constitutes the bulk of referrals. Further important considerations are that cases of sensori-neural loss, most of which are picked up by 3 years of age, do not get confused with the trial (although prevalence does not stabilise until 9 years),[49] and in addition children under 3 have a different case-mix load with proportionately more recurrent AOM to OME history episodes. After 11 years there are few children left with the condition, and dosing schedules would be inappropriate. The watchful waiting period of 3 months prevents unnecessary treatment and costs for many of the milder cases secondary to viral infections and flu, and sets the trial at an appropriate level of equipoise for topical steroid treatment lasting 3 months. Using objective tympanometric criteria with printouts that can be verified independently considerably increases the precision of inclusion criteria and excludes the unilateral cases that are not considered appropriate to treat (because of lack of evidence for disability).

Applying the tympanometric criteria has been shown to be feasible in general practice,[47] and

gives a more objective marker of the presence of OME than clinical evaluation alone. We propose to use trained research nurses to reduce the burden on doctor time and encourage trial protocol compliance.

We have not included a pure tone audiometry (PTA) hearing level (e.g. worse than 20 dB HL in the better ear) as an entry criterion for three reasons: (1) poor validity and reliability at the younger end of the study age group, effectively excluding one-third of otherwise eligible trial entrants; (2) secondary care trials have not shown HL to be an effect modifier; and (3) for the generalisability to a primary care case-mix, for which it is both reasonable and appropriate to include some milder bilateral cases.

Exclusion criteria

- Children for whom the doctor and parents judge that there are over-riding concerns (e.g. about poor speech development) as to warrant referral, i.e. we are allowing routine referrals to ENT outpatients. We will carry out multidisciplinary pilot work with focus groups of GPs, nurses and input from our ENT specialist advisor to improve study satisfaction and compliance.
- Children who are otherwise identified at high risk of recurrent disease, e.g. Cleft palate, Down's syndrome, primary ciliary dyskinesia, Kartagener's syndrome and other immuno-deficiency states.
- Children with ventilation tubes (grommets) in place or listed for operation prior to randomisation.
- Children treated with systemic steroids in the previous 3 months, or having poorly controlled asthma.
- When there are concerns about the child's growth; there is a history of frequent epistaxis; or there is known hypersensitivity to mometasone (Nasonex).

Withdrawals

Children will be withdrawn from the study in the instance of any suspected adverse event occurring, or when it subsequently comes to light that they meet any of the above exclusion criteria.

Ethical arrangements

The potential benefits include complete resolution of symptoms for those receiving the active drug, more quickly than for the controls, and an overall reduction in recurrences, referral and possible sparing of surgery (grommets), as well as reduced analgesic and/or antibiotic consumption. The benefits to society include eventually more equitable and otherwise improved pro-active management of children with OME in primary care. This is where the bulk of such children are seen, and options are presently limited to ineffective, undesirable or poorly structured 'remedies' of antibiotics, decongestants, anti-histamines or counselling.[50] There are considerable possible savings to the NHS, particularly on referrals for this condition.[51,52] Given that this is an RCT for what is in effect an extra treatment in this setting, we will minimally 'interfere' with the patients' and practices' normal decision-making processes regarding treatments and use of services including referral.

The potential side-effects of steroids applied intranasally including stinging and epistaxis, are minor and relatively infrequent. We are using a steroid with low systemic effects (see Pharmacokinetics) and so are extremely unlikely to observe any adverse effects on growth over a 3-month time frame, and almost certainly not without the use of highly sophisticated techniques that detect bone microfractures and changes to bone trabecular architecture. Nevertheless, we propose to monitor this carefully throughout the trial using the clinical techniques of height and weight measurement, and updated Tanner charts. We have discussed issues around growth measurement and stopping the trial with a senior advisor at the MCA. Where there is reasonable clinical concern, the trial DMEC (to include lay and expert members, and an invited member of the drug company if considered appropriate) will evaluate clinical and trial details on a case by case basis, and seek further expert advice as appropriate. The outcome assessments are minimally invasive and easy to perform or administer by trained staff. Schering-Plough will provide the randomisation code and code break envelopes which will be kept in duplicate by the co-ordinating centre and Schering-Plough. (Not triplicate – with no copies for GPs to ensure blinding.) When an individual code needs unblinding the primary responsibility for this rests with the trial leader and project manager who will provide contact details for trial fieldworkers and patients. Adverse events will be reported to the MCA [Medicines Control Agency], the ethics committees and also the drug safety department of Schering-Plough. We will record and report all suspected clinical adverse events according to the ICH [International Conference on Harminisation] guidelines, and using ICH definitions. We will

provide a copy of condensed guidance draft 2, 15 October 2002 for all fieldworkers. We will record all the known minor undesirable effects (e.g. epistaxis, nasal burning) as denoted on the data sheet – but not report these anticipated minor effects unless they meet the ICH definition of a serious adverse event, e.g. epistaxis requiring hospitalisation. We will report any immediate serious or life threatening hypersensitivity, e.g. angioedema and anaphylaxis, within 24 hours. We will also report any suspected adrenal suppression. We will record all children's growth, but report only cases in which the doctor suspects drug-related growth retardation, or in which children have a *z* score of –2.67 on updated Tanner–Whitehouse charts after the commencement of treatment and up to 9 months later.

The trial proposal is being submitted for MREC [Multicentre Research Ethics Committee] approval in October 2002 with the new LREC [Local Research Ethics Committee] arrangements (Plymouth), with full documentation, patient and doctor information sheets, trial protocols and headed consent for parents to sign.

We are applying to the MCA for a DDX [Doctor and Dentist Exemption] to cover the use of Nasonex below the age of its product licence (under 6 years) and in the condition of OME. We will keep all trial documentation for a minimum of 15 years in accordance with guidelines for good research practice. We will follow established ethics guidelines for clinical trials.[53–55]

Pharmacokinetic properties

Mometasone furoate (Nasonex) administered as an aqueous nasal spray has negligible less than 0.1% bioavailability and is generally undetectable in plasma using a method with a quantisation limit of 50 pg/ml or 5×10^{-11} g/ml.[41]

Required sample size

For a standard two-sided alpha of 0.05 and beta of 0.2 assuming (a) 21% resolution of effusions in the intranasal steroid group, (b) resolution in 10% of the placebo group and (c) a 15% dropout rate and 3% uninterpretable tympanograms, we require 388 children.[30,47,56] This is a smaller difference in effect size than in the previous trial, and a difference smaller than this is unlikely to be of any clinical significance.[30] This sample would also allow us to detect modest (~15%) differences in actual surgery rates in our referral based models, amidst anticipated alteration in referral patterns. If the randomised sample constitutes 37% of the original sample enrolled (due to natural history effects, refusal and referral), then 1050 children need to be identified in practices for 3 months' watchful waiting.[47]

We will pilot and recruit over the first winter (September 2003 to March 2004) and continue the main phase over 3 years with 9 months of further follow-up, finishing by June 2007. We will commence in 20 practices, and aim to recruit a total of 40 practices for the first winter and 60 practices, or as appropriate, for the second and third winters. Estimates of recruitment rates are based on (1) the current referral study and a referral audit on a practice of 11,000: at approximately six persistent cases per year per practice,[34] (2) estimates from a Hampshire trial of OME and its recurrence in a practice audit of 13,000: at 8–10 practices over 3 years to recruit 70 persistent cases,[12] and (3) the van Balen study: at 57 practices over 2 years to recruit 162 patients.[47] Based on these studies, which used opportunistic recruitment, we estimate about 50 practices of 10,000 list size recruiting three cases per year would be sufficient. However, because we will also be using an audit and case finding approach for at risk children, we predict easily finding three persistent cases per 10,000 per year (from 40 at risk children per practice per year). Thus we have made very conservative assumptions and by using the MRC GPRF we will ensure robust opportunistic recruitment, because the Framework specialises in nurse-led recruitment methods, and we will continue to recruit until we reach our targets. Because of the marked seasonal variation and risk of persistence we will target screen during September and October and audit for additional recruitment over winter months.

Statistical analysis

Subgroup analyses

The secondary analyses will incorporate estimates of high, low and zero adherence and be stratified by age group.[57] Subgroups will only be formed on the basis of significant by-treatment interactions on only a small number of a priori likely variables. Interaction tests will thus include the following expected or known effect modifiers, as well as controlling for these as baseline effects if appropriate: age, sex, weight for age, season, atopic history, total clinical risk factor score, and the symptom profile indicators both for ventilation tubes and for adenoidectomy from the TARGET trial data on the basis of significant interactions.[58–61] We will also consider if we need to carry out specific analyses for the different subgroups of loss to follow-up.

Primary analysis

The primary analysis will be on an ITT basis. Estimates of effectiveness will be expressed as ORs with 95% CI for dichotomous variables (e.g. microtympanometric category, adverse events, etc.) and derived by log linear regression. We will use analysis of covariance (ANCOVA) to analyse the continuous variables [e.g. OM5–25 score (see Outcomes), children's time off school, etc.], transforming variables as appropriate and controlling for confounding variables if by chance they are significantly different between groups. Models will be built to assess the treatment main effect modifiers of clinical and sociodemographic measures, and control for all known and potential confounders when they are significantly different between groups. Modelling for impact on surgery rates, based on referral rates and thresholds, is necessary because of the large number of potential confounders in clinical management, and because this research will happen at a time of likely changing referral patterns due to the publication of the TARGET trial. We will use ANCOVA for all our important outcome measures at baseline, which provides adjustments for these as necessary.

Our main analysis will be based on children as the unit rather than ears.

Cost analyses

Primary economic research objective Steroid treatment itself has at least two economic research aspects that both relate to clinical effectiveness – the cost and the results of the proposed treatment in relation to the already existing methods. The first is the short-term relief from primary symptoms and direct consequences of the condition. The second is the long-term effects in terms of less disability and adverse reactions from treatment. This study is able to assess only short- to medium-term outcomes, but will be able to use short-term effects plus literature to model the long-term economic effects of disability and special training.

Costs, analyses, and models Unit costs will be applied to all health service resource use data applying national average costs for consultations, procedures and admissions. Drug prices will be obtained from the BNF. Lost parental income and other loss of time will be based on average UK income. Average annual total costs per child will be established at 9-month follow-up for direct health care.

Incremental CEA will be performed for the additional cost of avoiding a defined case of recurrent OME, a referral, and modelled for an avoided operation (see below), provided that we find significant differences between groups for clinical outcomes.[18,62,63] The CEA will be carried out incorporating sensitivity analyses and CEACs.

We will build health economic models with specified assumptions to evaluate NHS costs and cost-effectiveness of the intervention.

A key feature of the health service resource data is that we do not yet know what the effect of the TARGET trial will be on recruitment rates, hence the requirement to model health service resource use using different assumptions. We will include in our models an assessment of the impact on surgical rates based on TARGET trial data. We will stratify our analyses of children into those predicted to benefit from surgery and those for whom it would be deemed inappropriate. We will model for efficacy versus other primary care factors in the trial in reducing surgery rates.

Frequency of analysis We will test our sample size assumptions at 6 months. We will make a single analysis of 1-month efficacy outcomes after 3 years, and (3+) 9-month effectiveness outcomes at 3 years 9 months.

Outcome measures

Primary outcome measure

The proportion of children cleared of bilateral effusions at 1 month as determined by the modified Jerger classification, i.e. children for whom there is resolution in one or both ears versus persistent bilateral cases. We have chosen 1 month to establish the short-term efficacy of the intervention – this timescale is based on the fact that previous evidence has shown an effect at 1 month.[30] We will perform otoscopy before all tympanometric measurements to exclude wax and perforations. We will use mini tymps with printout readings.

Secondary clinical outcome measures

- Timing of follow-up (as above at 3 months and 9 months). We have included a 3-month assessment to confirm or otherwise short-term effectiveness at the end of a feasible treatment period of 90 days (see Planned interventions). Any longer than 9 months will mean some children will be affected by a second natural wave of recurrence which would be expected to limit assessment of maximal benefit. As regards surgery rates, actual surgery may occur beyond a 9-month follow-up time frame; however, 9 months is a sufficient window to

catch trial treatment-failure referrals (using referral letters). For the economic retrospective analyses we will include the 3-month watchful waiting period, giving a total of 12 months from identification (see below).

- We will use the modified OM5–25 sensitive and responsive 25-item measure based on the large TARGET trial population (400 confirmed, 500 unaffected cases).[64] It is the best available instrument to reflect aspects of otitis media disease and impact when the diagnosis is OME. The five sequentially related dimensions are: physical health (respiratory and ear infections, seven included items); sleep disturbance (three); behaviour (six); impact on parent QoL (four); and reported hearing disability (four). M5–25 is primarily a succinct condition-specific measure of broad impact including health and behaviour in otitis media. Additionally, the seven physical symptom questions within it, on respiratory and ear infections, also permit two treatment indicators to be scored (see Subgroup analyses). These indicators are symptom profiles that predict children receiving markedly greater (or less) benefit from ventilation tubes and, separately, ability to benefit from adenoidectomy.[65] Epidemiological evidence suggests that they can do so because they select for particular host susceptibility at the pathogenetic stages upon which these treatments can act.[66] Thus we hypothesise they may also predict benefit from steroids.[67] As the major contributor to selection for effectiveness is non-resolution in untreated cases, the indicator scores can also be seen as composite risk factors for persistence of the condition, a validation that has been directly confirmed. The indicators' predictive value was replicated on independent data within TARGET as significant by-treatment interactions.[65]
- Measurement of selected individual ear symptoms over time including earache, hearing and balance symptoms will denote symptomatic resolution and recurrence, and their severity will be recorded by using a short 1- to 2-month symptom diary (handed out at entry and 1 month) incorporating Likert scales. These will be derived from the TARGET symptom and OM trial databases.[14,15,64] We will also measure initial visit-specific satisfaction and anxiety.[44] Assessment of validated frequency of repeat exacerbations will necessarily include tympanometric examination (see above) and audit of the notes for OM-related consultations. Beyond the 3-month treatment period we will use a single episode/event A4 sheet for parents to record further symptoms or significant health-related resource use for our economic evaluations – see below. We will also audit the notes to cover the period from identification through trial entry to final assessment at 9 months (3 + 9 months: the study year).
- We will measure NHS resource use and cost as measured by OM-related GP, nurse and health visitor consultations, relevant outpatient consultations for ENT and audiology, related hospital admissions and episodes of surgery (inpatients or day case to include listing for surgery and type). All non-trial medication costs for the 9-month follow-up and 3-month watchful waiting period will be estimated for all antibiotic courses, analgesics, decongestants and antihistamines using cost-assessing strategies in the parent diaries and A4 sheet, and through audit. Although the main economic analysis will assess costs from the perspective of the health service, we will also measure parents' salaried and unsalaried productivity loss as well as children's time off school over 12 months (3-month watchful waiting and 9-month follow-up). The latter also impacts on child development and QoL. We will have comparator estimates from audit information and parent questioning at randomisation for the previous (3+) 12 months.
- We will monitor all reported adverse events (e.g. stinging, epistaxis) and their frequency. We will use children's growth charts as currently updated to record height and weight at 1, 3 and 9 months.
- Compliance/adherence outcomes: we will include before and after bottle weight differences at 1 month and 3 months. We will then more accurately estimate compliance in individuals by seeing if the weight differences we measure tally with their reported adherence (questionnaire results).
- Trained nurses will evaluate otoscopic appearances at 1, 3 and 9 months using the TARGET otoscopy recording sheets.[68] We will not use the more complex and difficult technique of pneumatic otoscopy, which is currently not used in routine practice in the UK.
- PTA: we will measure children's hearing as impaired/non-impaired if hearing in the better ear at 0.5, 1 and 2 kHz is worse than or equal to 25 dB HL at 1, 3 and 9 months. We will use the Weber and Rinne tuning fork tests to confirm air–bone gaps and worst ear. We will apply

these tests in an age appropriate, validated manner to the children aged 5 years and over (approximately two-thirds of trial cohort).
- Numbers of children not reaching primary end point and differences between groups (study withdrawals with reasons for these).

For a linear time sequence of the trial flow procedures please see Appendix A.

Management of trial

We will seek advice and guidance from the HTA about whom to invite as an independent chair for the TSC. We will enlist a second independent member and routinely invite named observers from the HTA. As the fieldwork is being carried out at the GPRF for this multicentre trial and being run from Southampton, we propose to alternate meetings between London and Southampton over the 4-year trial period. Nine meetings in total spread out in a strategic time frame, as employed by most large trials.

We propose regular central trial management reviews. Data monitoring and ethics meetings will occur before the trial, 6 months after onset, at the mid-point and at the end. We will arrange any additional meetings and visits on an as needed basis. We will not issue GPs with code breaking envelopes, so that all suspected adverse events are reported to the co-ordinating centre where the decision will be made whether or not to approach the drug company to break the code and inform the doctor. Responsibility for trial data security belongs to University of Southampton.

Project timetable and milestones

1. We are currently starting to pilot identification of children at risk through practice audits in a factorial RCT of probiotics and xylitol in recurrent AOM in Hampshire practices. We will develop the audit schedule for nurses based on this and TARGET and PEPPER [Persistent Ear Problems – Promising Evidence for Reference] studies.
2. By December 2002 we aim to have obtained a DDX from the MCA as well as MREC approval (Plymouth), and cascaded to all relevant LRECs for approvals.
3. We will ensure that we have supplies of medication and placebo delivery set 6 months ahead of the planned trial commencement date, i.e. March 2003 for September 2003.
4. We will have taken central delivery of the microtympanometers and PTAs from Starkey Ltd. Ready for nurse instruction and distribution by the summer of 2003.
5. We will have produced and piloted all relevant training material for the research nurse study days, including trial protocols and management packs, by 1 August 2003. These will include diaries, OM5–25, etc. We will train nurses from participating practices on specially run courses in London between August and October 2003.
6. We will commence recruitment from the start date of 1 September 2003. We will carefully monitor any adverse events. We estimate recruiting 80–100 patients from 40 practices over the winter, i.e. by January and February 2004 (end of 3-month observation).
7. We anticipate seasonal variation in recruitment but at the rate of three randomised persistent cases per practice per year. We will make increased efforts, if appropriate, to identify at risk children and include further pro-active practices based on the 6-month evaluation for the first winter (March 2004). We anticipate including a further 20 practices i.e. 60 total for the second and third winters. (This will be preceded by further training courses for nurses in London as appropriate, for the third wave of 20 practices.)
8. We anticipate recruitment to terminate by the end of May 2006. We will analyse short-term outcomes by September 2006.
9. By the end of February 2007 the 9-month follow-up will be complete.
10. Analysis and report writing will be completed for the cost-effectiveness outcomes by the end of August 2007.
11. The mixture of expertise of the applicants will ensure the appropriate and effective dissemination of the trial results on completion.

Training and assessment of reliability (pre-trial, and first 6 months of recruitment)

We will commence study training in MRC interest-selected practices prior to the clinical commencement in September, in 20 practices (in two groups) – making best use of specific MRC training materials (e.g. video) and an established GPRF training centre. We will have already piloted a similar recruitment mechanism in a current trial in recurrent AOM. We will confirm our estimated recruitment in the first 20 practices over the first 12 weeks, while proceeding on a rolling basis to recruit trained and informed second wave less selected

practices (+20) for the first study winter, which will also provide improved study size recruitment estimates. More practices will be recruited for the second winter if our estimates from the first wave of practices recruit fewer patients than expected. We will review the diagnostic test characteristics by collaborating with senior community medical officers trained in audiology performing microtympanometry and PTA as the gold standards. We will assess the level of agreement beyond chance of the research nurses post-training in these techniques with these standards (kappas) and also assess the inter-rater reliability for a sample of this group.[69,70] The research nurses will perform community audiometry in full. To assess reliability we will sample the test site background noise using a sound pressure level meter, and employ a recognised adjustment to improve validity.[71,72]

Expertise

Applicants

Ian Williamson Trial project leader. Expertise in the field of OME including natural history and outcome measure development. Experience leading RCT in primary care in acute sinusitis, and a contributor to other major primary care health service trials in the respiratory field/team member of MRC/DH PEPPER referral study in OME. Lead supervisor of research assistant/PhD student for project.

Håkan Brodin Health economist. Expertise in the field of health technology assessment, especially the area of detailed primary research costing of health-care procedures.

Peter Robb Consultant ENT surgeon with a special interest in OME and paediatric ENT. Secondary care adviser to the project. MRC OME Group clinical investigator for the adjunct risk factor study to TARGET. Secretary of the British Association for Paediatric Otorhinolaryngology.

Mark Haggard Hearing researcher, psychologist and project leader for MRC/DH PEPPER study and for the TARGET trial; and advisor to many journals and public bodies on otitis media (e.g. NICE, Recent Advances, etc.). Expertise in statistical analysis of cohort studies and trials, and in questionnaire development and dissemination.

Paul Little Clinical trialist in health service research. Experience of running large trials in the same field, including factorial trials. Produced relevant trial materials, and principal investigator for trial databases central to this trial, e.g. AOM trials.

Mark Mullee Statistician, will provide statistical advice to the trial, and has advised our group on previous trials of otitis media.

Collaborators

Madge Vickers Head of the MRC GPRF. Considerable experience of running large studies based in primary care and using long-term outcomes. Responsibilities will be to facilitate access to the general practices, advise on the conduct of the trial and oversee the quality control.

Jeanette Martin Senior nurse manager for the MRC GPRF at the MRC Clinical trials Unit, London. She has responsibility for the nursing activities within the Framework and her team will be involved in developing nursing training and the standard operating procedures, and managing the quality control for the study.

Team member

Research assistant To be based at Southampton, will have responsibilities for day-to-day overall trial co-ordination (not GPRF fieldwork), production of all trial documentation, liaising with the GPRF senior nurse, central data collection and entry, quality standards (e.g. tympanometry), producing trial materials, general trouble-shooting, patient interviews and focus groups, randomisation list and protocol coordination and adverse event monitoring. He or she will be expected to help with the data analysis, report writing, papers and presentations suitable for a PhD.

Company contact

Tamsin Dight Medical affairs manager, Schering-Plough Ltd. Assistance with randomisation, concealment, production and randomisation of active treatments and placebos. Overseeing company provision of trial supplies and holder of confidentiality agreement with University of Southampton. Consultant on company recommendations, e.g. on nasal delivery and help with information sheet.

Expected output of research

The trial team intend to make maximal use of the supporting structures for the trial and broader potential interest groups in dissemination of key research findings. We envisage that this will primarily be in assisting practice teams to manage OME children more effectively, and particularly in the clarification of the role of nasal steroids in improving outcomes and parent satisfaction, and in reducing inappropriate referrals, at a time when demand and referrals are likely to be increasing. We will be introducing feasible technologies

into opinion-leading practices with considerable potential to reduce unnecessary diagnostic uncertainties here and efficiently seek out (thus reducing inequities) the appropriate children for the appropriate *remedies*. This trial will also allow development of research capacity through skills transfer on a number of different levels, and thus constitute payback. The data will be presented at national and international meetings, and published in peer-reviewed journals. Copies of the paper will be sent to the MeReC Bulletin and the Drugs and Therapeutics Bulletin. A report will be prepared for the HTA, and a summary of the report sent to magazines that doctors read (e.g. *GP*, *Doctor*, *Pulse*).

Justification of the support requested

We will be using the GPRF with costs over 4 years and 60 practices which include training, travel, consumables and mostly research nurse time. The decision is based on the essential need for a robust and reliable network that can deliver, against the general backdrop of problems with opportunistic recruitment of patients by GPs into research studies.

The trial equipment, namely microtympanometers and audiometers, are absolutely essential for this trial to be recognised at the appropriate level by the scientific establishment – for the standards we are using – and by subsequent Cochrane reviews. The use of mini-tymps with printouts is fully justified on the basis of validity checks and training issues. We are using an established and reliable company, Starkey Laboratories Ltd, based in Stockport, who agreed to a 20% discount for our bulk order of 60 MTP 10 mini-tymps with inbuilt audiometers. We propose that the eventual donation of this equipment to the practices will improve patient satisfaction, the NHS infrastructure in primary care, and also motivation and study compliance through a sense of ownership.

We require a research assistant at the appropriate grade suitable for completion of a PhD, depending on age and previous experience, for 4 years. This post will require someone with management capabilities. Our institution will require 40% on costs.

We require a part-time secretary based at Southampton (Cle 3 [Clerical Assistant Grade 3]) for 1 day per week with the same on costs.

Health economist time also needs to be purchased, given the high level of demand for senior health economists' time and our requirements for 1 day per week for 1 year (distributed over 4 years) plus on costs. We have also included consultancy fees for our statistician.

Stationery, telephone and trial materials are needed for the host institution and are important for our outcome measures.

Computer and software with appropriate statistical packages are needed for the research assistant and our trial database.

We estimate that we need 10 steering meetings at £100 per person for this national trial, and also some reserves for consultancies.

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Appendix A

Trial flow list of procedures

Case identification

GP, HV, Nurse refer case to *R*esearch *N*urse at *1* (sequence point) appointment.

RN uses 'continuous' audit protocol to identify and invite by telephone or post – approximately 3000 invitations in total to at-risk children.

RN1

- Patient/parent attend nurse for otoscopy/microtympanometry appointment. Trial management of otitis media discussed (10 minutes per patient). Total 1050 bilateral agree to watchful waiting.
- 1050 telephone calls or postcards 1 week before next appointment.

RN2

- 3 months' watchful waiting complete. Otoscopy/microtympanometry. 52% persistent bilateral or 546 cases (10-minute appointment) identified. Local GP and trial fax/telephone hotline support on interpretation of tympanograms.
- 158 not randomised. 28 referred to ENT. 130 refuse consent.
- *388–400 agree to randomisation* (rounded figures and assuming no further dropouts for costings) (+30 minute appointment). Informed consent taken. Randomised in blocks of four.
- Baseline measures in 400.
- Demographic details.
- History including previous 15-month attendance/antibiotic/analgesic consumption.
- PTA.
- Height and weight.
- OM5–25.
- Instructions on trial use of medications.
- Make 1-month appointment with RN.
- At 7 days 400 telephone calls for assistance with questionnaire/diary completion. Check concealment. Use of short form adapted adherence questionnaire.
- Reminder postcard 1 week before appointment due.

RN3

- 1-month outcome measures. 400 (30-minute appointment).
- Medication review adherence, adverse events, check symptom diaries completed, audit analgesic antibiotic use, monitor referral and outcomes.
- OM5–25.
- Otoscopy/microtympanometry.
- PTA.
- Height, weight.
- Instructions on medication repeated.
- Make 3-month appointment.

- Post baseline and 1-month data and trial medication to Southampton.
- Make second appointment for non-responders. (Up to two further telephone calls and two postcards.)
- Follow-up dropouts with tel. with reasons.
- Assistance/adherence telephone call at 1 month 1 week. Reminder to attend by postcard before 3 months.

RN4
- 3-month outcome measures in 400 (30-minute appointment).
- Medication review adherence adverse events, check symptom diary, audit analgesic antibiotic use, monitor referral and outcomes.
- OM5–25.
- Otoscopy/microtympanometry.
- PTA.
- Height, weight.
- Instructions on medication.
- Schedule final 9-month appointment.
- Post 3-month data and trial medication to Southampton.
- Make second appointment for non-responders (up to two further telephone calls and two postcards).
- Follow up dropouts with telephone calls with reasons.
- Reminder telephone calls/postcards for RN5 at 9 months.

RN5
- 9-month outcomes in 400 (30-minute appointment).
- Check symptom/events sheet, e.g. time off work, recurrent episodes, antibiotics, analgesics.
- Monitor referral letters, OPD appointments, listed or actual surgery through practice audit.
- OM5–25.
- Otoscopy/microtympanometry.
- PTA.
- Height, weight.
- Exit interview to include treatment preferences.
- Post trial data and final audit data to Southampton.

Second version, 16 June 2004

The University of Southampton

Title

A double-blind randomised placebo-controlled trial of topical intranasal steroids in 4- to 11-year-old children with persistent bilateral OME in primary care.

How has the project changed since the outline proposal was submitted?

The project has been critically developed from outline to a full submission by incorporating the most recent research findings, both published and unpublished. In particular we have taken heed of the reviewers' general feedback to address the brief's requirements in relation to cost-effectiveness, by developing the overall trial methodology and analyses towards longer term outcomes important to the NHS.

Planned investigation

Research objectives

1. To assess the effectiveness, and cost-effectiveness, of topical intranasal steroids over 1 year (in total) in a pragmatic clinical trial.
2. 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.

Introduction

Otitis media with effusion is an almost universal condition of childhood, and in its chronic and recurrent forms is a source of substantial NHS costs, with over £200M per year spent on related otitis media prescribing, and an additional £30M in costs to the NHS for grommets, the operation used to treat the more persistent and/or severe cases. The majority of children are referred from primary care, but confusions over treatment and uncertain diagnosis here 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 to curb the processes of referral. Now, with the about to be published findings of substantial benefit from surgery from the trial of alternative regimens in glue ear treatment (TARGET), albeit in selected cases, rates look set to rise again, unless primary care management becomes more effective for this problem. Currently, however, there are no effective treatments available in primary care, thus the requirement to develop them is now urgent.

Existing research

Otitis media with effusion treatments have been, and are being, extensively reviewed (*BMJ Clinical Evidence*, Cochrane reviews on steroids, grommets, antibiotics) because OME is a source of substantial morbidity in children, and considerable costs to the NHS.[1–6] It leads to hearing loss, delays in language and behaviour development, and is

the commonest reason for surgery in children.[7,8] While the TARGET trial is currently clarifying the role for surgery in restricted and persistent cases, there is, and is likely to remain, a need for medical treatments for temporising management, or as an alternative or adjunct to surgery.[9,10] The aims of interventions should be to secure improvement in hearing and well-being of affected children and to minimise poor behavioural, speech and educational outcomes.[1] As OME is a highly recurrent condition with a mean duration of 6–10 weeks, outcomes need to be evaluated over a reasonable 6-month to 1-year period.[11–13] Few quality studies of any treatment have followed up children beyond 3 months, and very few address more child-centred outcomes and QoL issues.

The use of a well-validated QoL measure is essential in addition to tympanometry and audiometry as there may not be a close relationship between these observed outcomes and the reported QoL.

Secondary research has allowed a re-evaluation of the benefits of antibiotics in OME showing 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 2002). Furthermore, prescribing antibiotics encourages belief in them, re-attendance, and increasing antibiotic resistance in strains of *Streptococcus pneumoniae*.[14–17] Side-effects, costs and substantial compliance issues for longer three or four times a day courses render them now untenable as a treatment for OME.

The use of *systemic* steroids has been recommended in combination with antibiotics as cost-effective in OME, but this is based on a low quality meta-analysis, which included trials rejected by the Cochrane review.[18] 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.[19] These concerns in the absence of better evidence of sustained and worthwhile effect from the small and heterogeneous trials included in Cochrane effectively preclude their use for a mild condition with an episodic natural history such as OME.[20–27] Thus on a priori grounds, *topical* intranasal steroids are a logical treatment for evaluation in OME. Our group has been interested in this possibility since the early 1990s, following on from Berman's work. There are several theoretical bases for topical intranasal treatment, and these include phospho-lipid membrane and decongestant/anti-inflammatory effects to the nasal mucosa.[28,29]

This therapeutic approach has now been identified as of value by the Cochrane review of topical intranasal steroids in OME (date of last search January 2002). The review, however, does not recommend use of topical nasal steroids, because of insufficient high quality evidence, although the favourable trial by Tracy and Demain[30] was highly rated on methodological criteria.[31] This trial included only 61 children, and was set in a military airbase in the USA, possibly 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 referred 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 can 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, taking into account the relatively slow resolution of OME, should preferably be given for several months. Serious side-effects for inhaled topical steroids are rare, but there are concerns that growth may be affected.[32] This makes it imperative that a topical steroid is chosen with minimal systemic effects.

We are aware of an unpublished double-blind RCT of Flixonase in children aged 4 years and over from a tertiary care setting.[33] The trial has good adherence over 2 years and appears effective in preventing recurrences of OME in a severe case-mix group. There are, however, no RCTs from a UK primary care population, hence treatment effects are unknown in the real setting where watchful waiting occurs, and thus there is no evidence base to guide the optimal management of the bulk of significant but proportionately milder cases (differences of case-mix limits generalisability to primary care, from secondary care trials). Any trial on cost-effectiveness needs to consider which groups are most likely to benefit. Thus we aim 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 watchful waiting) and in the group most likely to be referred (i.e. 3 years and over). Medical treatment in these groups is most likely to impact on NHS resource use. To increase the robustness and stringency of the trial we will use microtympanometry. We will be evaluating such improved systems of waiting and treatment for affected children and their families at a time when demand for surgery is likely to be rising again as a result of the TARGET findings and policy expectations of the NHS (changing patterns and an overall increase in referrals). Thus, an NHS trial should not only document referral rates in long-term follow-up but also assess the potential impact of different referral rates and thresholds on management and surgery using modelling techniques.

In summary, we think this review of the evidence makes it clear that there is need for a trial of nasal steroids in OME that has the following features:

- children with persistent bilateral effusion
- follow-up in the medium term (more than 6 months)
- addresses validated child-centred outcomes (e.g. QoL issues) in addition to audiometry and tympanometry
- use a treatment with low systemic absorption, for at least 3 months during the winter months
- assess benefit in those children who are most likely to be referred (i.e. 3 years and over)
- assesses health service resource use and models the impact of likely changes in referral pattern.

Research methods

A double-blind randomised placebo-controlled trial. The main analysis will be on an ITT basis.

Setting

The proper setting for the trial is primary care, and so to achieve generalisability we aim to recruit from 60 practices throughout the UK. We plan to utilise the MRC GPRF to ensure high quality standards in recruitment and follow-up.

Target population

Children aged between 4 and 11 years will be identified from participating practices, through new and follow-up doctor/health-visitor or nurse consultations for current suspected OME, and from regular audit of the notes. The proposal is to identify children who have persistent bilateral effusion, i.e. with abnormal tympanometry in both ears which has persisted for 3 months. Children will be identified for screening with tympanometry in the following ways:

- A monthly search of notes will be made during the autumn and winter months (September through to February) for children presenting to the GP or nurse where the diagnosis is made of OME
- Nurses will also identify two broad types of at-risk children. They will use established search methods applied to the notes in September and October of each study recruitment year. Type 1 children will be identified by typical OME histories from the notes, i.e. those with identified hearing loss, snoring, behaviour, speech and 'educational concerns' consultations. One, two or more such ear *problem* consultations identified over the preceding 12 months will constitute sufficient risk for screening.[34]
- Type 2 children are otitis-prone children (AOM), who will be similarly identified but on the reported frequency of all otitis media episodes. Otitis-prone children are well recognised at being at high associated risk of developing OME.[35] There is no agreed definition of otitis proneness: we have chosen one, two or more otitis media labelled episodes (separated by 2 weeks from each other) over the 12 preceding months as a pragmatic definition of proneness because (1) we will be recruiting going into winter, so need to look at the previous winter, (2) we want to include most at risk children as we will be screening not treating and (3) this is still a small minority of children with otitis media and thus will not have great workload implications.[36]

We will proceed to carry out monthly audit and assessment for the subsequent winter months (up to February) to pick up any new episodes or missed cases. All children so identified (with the bulk at the beginning of the autumn term) will require tympanometric confirmation of bilateral OME on two occasions 3 months apart using the modified Jerger classification (B + B, B + C2).[37,38]

Randomisation

We have discussed concealment issues with the manufacturers (Schering-Plough). The company will use computer-generated random number lists using formula-generated sequences from pre-specified software input, in order to sequence randomised treatment blocks of four (two with active treatment, two with placebo). These will be

distributed to trial personnel who are blind to the medication, supplied as estimated and required. We will ensure that double-blinding is total and effective so that the research nurse can pick the next trial pack from the tray and log that they have done so using a unique medication ID and a unique child ID number. The company will keep the randomisation code at a distant site, and so does not propose the more logistically complex and costly telephone randomisation method as offering any advantages.[39,40]

Health technologies being assessed
Patients meeting entry criteria and giving full informed consent will be randomised to receive placebo or topical intranasal steroids given once a day for 3 months. We will use mometasone 50 µg in each nostril (total daily dose 100 µg) because of its low systemic absorption and specified safety profile.[41–43] The trial will be organised as an adjunct or extra to usual treatment of such children by the practice (see Ethics section).

Protection against other sources of bias
Recruitment bias will be assessed by asking GPs and nurses to keep a simple tally and log of all patients consulting with the condition and to tick boxes for the five categories of loss to follow-up in randomised trials: refusal of randomisation, rejection of treatment path, logistical reasons (e.g. intended house moving), other reasons and DNAs. The reason for not recruiting will be recorded in the log book. We will include ENT referrals over this period as an important reason for non-entry. Brief clinical characteristics of those not entered will be documented and their postcode will provide gross information on material deprivation. We will use a post-study questionnaire to find out why the lowest recruiting GPs did not recruit.[44]

We will ensure that treatment and placebo taste as similar as possible, and will evaluate concealment by testing placebo/treatment recognition by asking parents by telephone at 7 days, before any treatment effects would be expected. We will also ask them at the end of the trial to estimate placebo effects. The investigators, GPs and nurses will be kept blind to the allocation throughout the duration of the trial except in the event of adverse reactions (see Ethical arrangements). We will test randomisation by assessing the distributions of important prognostic factors by group.

We will quantify response bias by comparing the same important clinical predictors in those completing the study at 9 months and those lost to follow-up (for potential effect modifiers see Subgroup analyses). We estimate less than 5% loss to follow-up at 3 months and less than 15% at 9 months because we envisage parents/children will be motivated and we are using a reliable network.[45]

Interventions
Topical intranasal steroids: mometasone furoate 50 µg in each nostril once daily for 3 months versus placebo in each nostril once daily for 3 months. The appropriate method of using the spray with the chin-up will be demonstrated and assessed so that the maximal dose to the posterior nasal space is achieved. This is 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. We will supplement this with a succinct illustrated patient information sheet on aims, use, safety and side-effects. We will evaluate compliance by measuring before and after individual bottle-weights. We will use non-directive questioning, e.g. 'Have you any concerns or experienced any problems with this medication?', at follow-up nurse clinic and telephone interviews, based on a modified brief adherence questionnaire.[46] In our considerations of duration and compliance we note that two trials have achieved effective compliance for 3 months and 2 years respectively using topical steroids, albeit from secondary care.[30,33] In addition we have successfully piloted a study of children taking nasal sprays versus placebo spray and had only one dropout in the trial of 21 children, from non-acceptability of the spray in a child aged 4 or over. A shorter course, i.e. 2 months, would have less impact on recurrence, whereas the timing of the end of watchful waiting for January/early February will mean that a subsequent 3-month course has the potential in terms of cost-efficiency both to prevent some early recurrences (secondary to seasonal viral infections and atopy), and also to better cover the natural incidence peak in the spring term.[12] Any longer than 3 months would introduce greater complexities in relation to administration, would increase side-effects, might delay important management decisions in relation to children identified 6 months earlier and does not take account of the strong seasonal resolutional effects around this time.[9,12] We are using a once daily dosing schedule to encourage compliance.

Inclusion criteria
Children aged between 4 and 11 years old identified by participating practices and have bilateral OME on tympanometry on two occasions 3 months apart; using the modified

Jerger classification (B + B, B + C2).[37,38,47] A B tympanogram has a positive predictive value of 84%, and a C2 of 54%.[48]

Thus children who have persistent effusions after a 3-month period of watchful waiting, who do not meet exclusion criteria and whose parents consent will be entered. The treatment may feasibly be taken by children as young as 3 years. Although children younger than 3 may benefit, delivery of nasal steroids is more problematic, and cost-effectiveness needs to be demonstrated in the older group first, which constitutes the bulk of referrals. Further important considerations are that cases of sensori-neural loss, most of which are picked up by 4 years of age, do not get confused with the trial (although prevalence does not stabilise until 9 years),[49] and in addition children under 4 have a different case-mix load with proportionately more recurrent AOM to OME history episodes. After 11 years there are few children left with the condition, and dosing schedules would be inappropriate. The watchful waiting period of 3 months prevents unnecessary treatment and costs for many of the milder cases secondary to viral infections and flu, and sets the trial at an appropriate level of equipoise for topical steroid treatment lasting 3 months. Using objective tympanometric criteria with printouts that can be verified independently considerably increases the precision of inclusion criteria and excludes the unilateral cases that are not considered appropriate to treat (because of lack of evidence for disability).

Applying the tympanometric criteria has been shown to be feasible in general practice,[47] and gives a more objective marker of the presence of OME than clinical evaluation alone. We propose to use trained research nurses to reduce the burden on doctor time and encourage trial protocol compliance.

We have not included a PTA hearing level (e.g. worse than 20 dB HL in the better ear) as an entry criterion for three reasons: (1) poor validity and reliability at the younger end of the study age group, effectively excluding one-third of otherwise eligible trial entrants; (2) secondary care trials have not shown HL to be an effect modifier; and (3) for the generalisability to a primary care case-mix, for which it is both reasonable and appropriate to include some milder bilateral cases.

Exclusion criteria

- Children who are otherwise identified at high risk of recurrent disease, e.g. Cleft palate, Down's syndrome, primary ciliary dyskinesia, Kartagener's syndrome and other immuno-deficiency states.
- Children with ventilation tubes (grommets) in place or listed for operation prior to randomisation.
- Children treated with systemic steroids in the previous 3 months, or having poorly controlled asthma.
- When there are concerns about the child's growth; there is a history of frequent epistaxis; or there is known hypersensitivity to mometasone (Nasonex).

Withdrawals

Children will be withdrawn from the study in the instance of any suspected adverse event occurring, or where it subsequently comes to light that they meet any of the above exclusion criteria.

Ethical arrangement

The potential benefits include complete resolution of symptoms for those receiving the active drug, more quickly than for the controls, and an overall reduction in recurrences, referral and possible sparing of surgery (grommets), as well as reduced analgesic and/or antibiotic consumption. The benefits to society include eventually more equitable and otherwise improved pro-active management of children with OME in primary care. This is where the bulk of such children are seen, and options are presently limited to ineffective, undesirable or poorly structured 'remedies' of antibiotics, decongestants, anti-histamines or counselling.[50] There are considerable possible savings to the NHS, particularly on referrals for this condition.[51,52] Given that this is an RCT for what is in effect an extra treatment in this setting, we will minimally 'interfere' with the patients' and practices' normal decision-making processes regarding treatments and use of services including referral, i.e. the intervention is nasal spray plus standard management versus placebo spray plus standard management. Standard management in this context may include further watchful waiting, nose drops, antibiotics and referral as per usual doctor practice.

The potential side-effects of steroids applied intranasally including stinging and epistaxis, are minor and relatively infrequent. We are using a steroid with low systemic effects (see Pharmacokinetics) and so are extremely unlikely to observe any adverse effects on growth over a 3-month time frame, and almost certainly not without the use of highly sophisticated techniques

that detect bone microfractures and changes to bone trabecular architecture. Nevertheless, we propose to monitor this carefully throughout the trial using the clinical techniques of height and weight measurement, and updated Tanner charts. We have discussed issues around growth measurement and stopping the trial with a senior advisor at the MCA. Where there is reasonable clinical concern, the trial DMEC (to include lay and expert members, and an invited member of the drug company if considered appropriate) will evaluate clinical and trial details on a case by case basis, and seek further expert advice as appropriate. The outcome assessments are minimally invasive and easy to perform or administer by trained staff. Schering-Plough will provide the randomisation code and code break envelopes which will be kept in duplicate by the co-ordinating centre and Schering-Plough. (Not triplicate – with no copies for GPs to ensure blinding.) When an individual code needs unblinding the primary responsibility for this rests with the trial leader and project manager who will provide contact details for trial fieldworkers and patients. Adverse events will be reported to the MCA [Medecines Control Agency], the ethics committees and also the drug safety department of Schering-Plough. We will record and report all suspected clinical adverse events according to the ICH guidelines, and using ICH [International Conference on Harmonisation] definitions. We will provide a copy of condensed guidance draft 2, 15 October 2002 for all fieldworkers. We will record all the known minor undesirable effects (e.g. epistaxis, nasal burning) as denoted on the data sheet – but not report these anticipated minor effects unless they meet the ICH definition of a serious adverse event, e.g. epistaxis requiring hospitalisation. We will report any immediate serious or life threatening hypersensitivity, e.g. angioedema and anaphylaxis, within 24 hours. We will also report any suspected adrenal suppression. We will record all children's growth, but report only cases in which the doctor suspects drug-related growth retardation, or in which children have a z score of –2.67 on updated Tanner–Whitehouse charts after the commencement of treatment and up to 9 months later.

The trial proposal is being submitted for MREC [Multicentre Research Ethics Committee] approval in October 2002 with the new LREC [Local Research Ethics Committee] arrangements (Plymouth), with full documentation, patient and doctor information sheets, trial protocols and headed consent for parents to sign.

We are applying to the MCA for a DDX [Doctor and Dentist Exemption] to cover the use of Nasonex below the age of its product licence (under 6 years) and in the condition of OME. We will keep all trial documentation for a minimum of 15 years in accordance with guidelines for good research practice. We will follow established ethics guidelines for clinical trials.[53–55]

Pharmacokinetic properties

Mometasone furoate (Nasonex) administered as an aqueous nasal spray has negligible less than 0.1% bioavailability and is generally undetectable in plasma using a method with a quantitation limit of 50 pg/ml or 5×10^{-11} g/ml.[41]

Required sample size

For a standard two-sided alpha of 0.05 and beta of 0.2 assuming (a) 21% resolution of effusions in the intranasal steroid group, (b) resolution in 10% of the placebo group and (c) a 15% dropout rate and 3% uninterpretable tympanograms, we require 388 children.[30,47,56] This is a smaller difference in effect size than in the previous trial, and a difference smaller than this is unlikely to be of any clinical significance.[30] This sample would also allow us to detect modest (~15%) differences in actual surgery rates in our referral based models, amidst anticipated alteration in referral patterns. If the randomised sample constitutes 37% of the original sample enrolled (due to natural history effects, refusal and referral), then 1050 children need to be identified in practices for 3 months' watchful waiting.[47]

We will pilot and recruit over the first winter (September 2003 to March 2004) and continue the main phase over 3 years with 9 months of further follow-up, finishing by June 2007. We will commence in 20 practices, and aim to recruit a total of 40 practices for the first winter and 60 practices, or as appropriate, for the second and third winters. Estimates of recruitment rates are based on (1) the current referral study and a referral audit on a practice of 11,000: at approximately six persistent cases per year per practice,[34] (2) estimates from a Hampshire trial of OME and its recurrence in a practice audit of 13,000: at 8–10 practices over 3 years to recruit 70 persistent cases,[12] and (3) the van Balen study: at 57 practices over 2 years to recruit 162 patients.[47] Based on these studies, which used opportunistic recruitment, we estimate about 50 practices of 10,000 list size recruiting three cases per year would be sufficient. However, because we will also be using an audit and case finding approach for

at risk children, we predict easily finding three persistent cases per 10,000 per year (from 40 at risk children per practice per year). Thus we have made very conservative assumptions and by using the MRC GPRF we will ensure robust opportunistic recruitment, because the Framework specialises in nurse-led recruitment methods, and we will continue to recruit until we reach our targets. Because of the marked seasonal variation and risk of persistence we will target screen during September and October and audit for additional recruitment over winter months.

Statistical analysis

Primary outcome

The primary analysis will be on an 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 will be compared using a logistic regression model with adjustment for four covariates: season (January–March versus the rest of the year); age at randomisation (continuous in months); atopy (defined as the combination of asthma/eczema/hay fever that best predicts outcome in a blind analysis of patients ignoring randomisation); and 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 previous 12 months, and adenoidal symptom score – identified in an analysis of these variables ignoring randomisation group).

Effect modification

Interaction tests will be carried out between randomisation groups and each of (1) age, (2) atopy and (3) clinical severity score – defined as above. In the event that these are statistically significant ($p < 0.05$), separate results will be presented in subgroups.

Secondary outcomes

Dichotomous outcome variables will be analysed using logistic regression models with results expressed as ORs with 95% CIs. Ordered categorical variables with more than two categories will be analysed using log linear models and trend tests. Continuous variables will be analysed using ANCOVA to adjust for baseline. All analyses will adjust for the four covariates described for the primary outcome variable. Subgroup results will be reported only if any of the interactions tests listed above were statistically significant.

Cost analyses

Primary economic research objective Steroid treatment itself has at least two economic research aspects that both relate to clinical effectiveness – the cost and the results of the proposed treatment in relation to the already existing methods. The first is the short-term relief from primary symptoms and direct consequences of the condition. The second is the long-term effects in terms of less disability and adverse reactions from treatment. This study is able to assess only short- to medium-term outcomes, but will be able to use short-term effects plus literature to model the long-term economic effects of disability and special training.

Costs, analyses, and models Unit costs will be applied to all health service resource use data applying national average costs for consultations, procedures and admissions. Drug prices will be obtained from the BNF. Lost parental income and other loss of time will be based on average UK income. Average annual total costs per child will be established at 9-month follow-up for direct health care.

Incremental CEA will be performed for the additional cost of avoiding a defined case of recurrent OME, a referral, and modelled for an avoided operation (see below), provided that we find significant differences between groups for clinical outcomes.[18,62,63] The CEA will be carried out incorporating sensitivity analyses and CEACs.

We will build health economic models with specified assumptions to evaluate NHS costs and cost-effectiveness of the intervention.

A key feature of the health service resource data is that we do not yet know what the effect of the TARGET trial will be on recruitment rates, hence the requirement to model health service resource use using different assumptions. We will include in our models an assessment of the impact on surgical rates based on TARGET trial data. We will stratify our analyses of children into those predicted to benefit from surgery and those for whom it would be deemed inappropriate. We will model for efficacy versus other primary care factors in the trial in reducing surgery rates.

Frequency of analysis We will test our sample size assumptions at 6 months. We will make a single analysis of 1-month efficacy outcomes after 3 years, and (3+) 9-month effectiveness outcomes at 3 years 9 months.

Outcome measures

Primary outcome measure

The proportion of children cleared of bilateral effusions at 1 month as determined by the modified Jerger classification, i.e. children for whom there is resolution in one or both ears versus persistent bilateral cases. We have chosen 1 month to establish the short-term efficacy of the intervention – this timescale is based on the fact that previous evidence has shown an effect at 1 month.[30] We will perform otoscopy before all tympanometric measurements to exclude wax and perforations. We will use mini tymps with printout readings.

Secondary clinical outcome measures

- Timing of follow-up (as above at 3 months and 9 months). We have included a 3-month assessment to confirm or otherwise short-term effectiveness at the end of a feasible treatment period of 90 days (see Planned interventions). Any longer than 9 months will mean some children will be affected by a second natural wave of recurrence which would be expected to limit assessment of maximal benefit. As regards surgery rates, actual surgery may occur beyond a 9-month follow-up time frame; however, 9 months is a sufficient window to catch trial treatment-failure referrals (using referral letters). For the economic retrospective analyses we will include the 3-month watchful waiting period, giving a total of 12 months from identification (see below).
- We will use the modified OM8-30 sensitive and responsive 25-item measure based on the large TARGET trial population (400 confirmed, 500 unaffected cases).[64] It is the best available instrument to reflect aspects of otitis media disease and impact when the diagnosis is OME. The five sequentially related dimensions are: physical health (respiratory and ear infections, seven included items); sleep disturbance (three); behaviour (six); impact on parent QoL (four); and reported hearing disability (four). OM8-30 is primarily a succinct condition-specific measure of broad impact including health and behaviour in otitis media. Additionally, the seven physical symptom questions within it, on respiratory and ear infections, also permit two treatment indicators to be scored (see Subgroup analyses). These indicators are symptom profiles that predict children receiving markedly greater (or less) benefit from ventilation tubes and, separately, ability to benefit from adenoidectomy.[65] Epidemiological evidence suggests that they can do so because they select for particular host susceptibility at the pathogenetic stages upon which these treatments can act.[66] Thus we hypothesise they may also predict benefit from steroids.[67] As the major contributor to selection for effectiveness is non-resolution in untreated cases, the indicator scores can also be seen as composite risk factors for persistence of the condition, a validation that has been directly confirmed. The indicators' predictive value was replicated on independent data within TARGET as significant by-treatment interactions.[65]
- Measurement of selected individual ear symptoms over time including earache, hearing and balance symptoms will denote symptomatic resolution and recurrence, and their severity will be recorded by using a short 1- to 2-month symptom diary (handed out at entry and 1 month) incorporating Likert scales. These will be derived from the TARGET symptom and OM trial databases.[14,15,64] We will also measure initial visit-specific satisfaction and anxiety.[44] Assessment of validated frequency of repeat exacerbations will necessarily include tympanometric examination (see above) and audit of the notes for OM-related consultations. Beyond the 3-month treatment period we will use a single episode/event A4 sheet for parents to record further symptoms or significant health-related resource use for our economic evaluations – see below. We will also audit the notes to cover the period from identification through trial entry to final assessment at 9 months (3 + 9 months: the study year).
- We will measure NHS resource use and cost as measured by OM-related GP, nurse and health visitor consultations, relevant outpatient consultations for ENT and audiology, related hospital admissions and episodes of surgery (inpatients or day case to include listing for surgery and type). All non-trial medication costs for the 9-month follow-up and 3-month watchful waiting period will be estimated for all antibiotic courses, analgesics, decongestants and antihistamines using cost-assessing strategies in the parent diaries and A4 sheet, and through audit. Although the main economic analysis will assess costs from the perspective of the health service, we will also measure parents' salaried and unsalaried productivity loss as well as children's time off school over 12 months (3-month watchful waiting and 9-month follow-up). The latter also impacts on child development and QoL.

We will have comparator estimates from audit information and parent questioning at randomisation for the previous (3+) 12 months.
- We will monitor all reported adverse events (e.g. stinging, epistaxis) and their frequency. We will use children's growth charts as currently updated to record height and weight at 1, 3 and 9 months.
- Compliance/adherence outcomes: we will include before and after bottle weight differences at 1 month and 3 months. We will then more accurately estimate compliance in individuals by seeing if the weight differences we measure tally with their reported adherence (questionnaire results).
- Trained nurses will evaluate otoscopic appearances at 1, 3 and 9 months using the TARGET otoscopy recording sheets.[68] We will not use the more complex and difficult technique of pneumatic otoscopy, which is currently not used in routine practice in the UK.
- PTA: we will measure children's hearing as impaired/non-impaired if hearing in the better ear at 0.5, 1 and 2 kHz is worse than or equal to 25 dB HL at 1, 3 and 9 months. We will use the Weber and Rinne tuning fork tests to confirm air–bone gaps and worst ear. We will apply these tests in an age appropriate, validated manner to the children aged 5 years and over (approximately two-thirds of trial cohort).
- Numbers of children not reaching primary end point and differences between groups (study withdrawals with reasons for these).

For a linear time sequence of the trial flow procedures please see Appendix A.

Management of trial

We will seek advice and guidance from the HTA about whom to invite as an independent chair for the TSC. We will enlist a second independent member and routinely invite named observers from the HTA. As the fieldwork is being carried out at the GPRF for this multicentre trial and being run from Southampton, we propose to alternate meetings between London and Southampton over the 4-year trial period. Nine meetings in total spread out in a strategic time frame, as employed by most large trials.

We propose regular central trial management reviews. Data monitoring and ethics meetings will occur before the trial, 6 months after onset, at the mid-point and at the end. We will arrange any additional meetings and visits on an as needed basis. We will not issue GPs with code breaking envelopes, so that all suspected adverse events are reported to the co-ordinating centre where the decision will be made whether or not to approach the drug company to break the code and inform the doctor. Responsibility for trial data security belongs to University of Southampton.

Project timetable and milestones

1. We are currently starting to pilot identification of children at risk through practice audits in a factorial RCT of probiotics and xylitol in recurrent AOM in Hampshire practices. We will develop the audit schedule for nurses based on this and TARGET and PEPPER [Persistent Ear Problems – Promising Evidence for Reference] studies. This study showed the acceptability and tolerability of nasal sprays in older children (4+ years) for otitis media.
2. By December 2002 we aim to have obtained a DDX from the MCA as well as MREC approval (Plymouth), and cascaded to all relevant LRECs for approvals.
3. We will ensure that we have supplies of medication and placebo delivery set 6 months ahead of the planned trial commencement date, i.e. March 2003 for September 2003.
4. We will have taken central delivery of the microtympanometers and PTAs from Starkey Ltd. Ready for nurse instruction and distribution by the summer of 2003.
5. We will have produced and piloted all relevant training material for the research nurse study days, including trial protocols and management packs, by 1 August 2003. These will include diaries, OM5–25, etc. We will train nurses from participating practices on specially run courses in London between August and October 2003.
6. We will commence recruitment from the start date of 1 September 2003. We will carefully monitor any adverse events. We estimate recruiting 80–100 patients from 40 practices over the winter, i.e. by January and February 2004 (end of 3-month observation).
7. We anticipate seasonal variation in recruitment but at the rate of three randomised persistent cases per practice per year. We will make increased efforts, if appropriate, to identify at risk children and include further pro-active practices based on the 6-month evaluation for the first winter (March 2004). We anticipate including a further 20 practices i.e. 60 total for the second and third winters. (This will be preceded by further training courses for nurses

in London as appropriate, for the third wave of 20 practices.)
8. We anticipate recruitment to terminate by the end of May 2006. We will analyse short-term outcomes by September 2006.
9. By the end of February 2007 the 9-month follow-up will be complete.
10. Analysis and report writing will be completed for the cost-effectiveness outcomes by the end of August 2007.
11. The mixture of expertise of the applicants will ensure the appropriate and effective dissemination of the trial results on completion.

Training and assessment of reliability (pre-trial, and first 6 months of recruitment)

We will commence study training in MRC interest-selected practices prior to the clinical commencement in September, in 20 practices (in two groups) – making best use of specific MRC training materials (e.g. video) and an established GPRF training centre. We will have already piloted a similar recruitment mechanism in a current trial in recurrent AOM. We will confirm our estimated recruitment in the first 20 practices over the first 12 weeks, while proceeding on a rolling basis to recruit trained and informed second wave less selected practices (+20) for the first study winter, which will also provide improved study size recruitment estimates. More practices will be recruited for the second winter if our estimates from the first wave of practices recruit fewer patients than expected. We will review the diagnostic test characteristics by collaborating with senior community medical officers trained in audiology performing microtympanometry and PTA as the gold standards. We will assess the level of agreement beyond chance of the research nurses post-training in these techniques with these standards (kappas) and also assess the inter-rater reliability for a sample of this group.[69,70] The research nurses will perform community audiometry in full. To assess reliability we will sample the test site background noise using a sound pressure level meter, and employ a recognised adjustment to improve validity.[71,72]

Expertise

Applicants

Ian Williamson Trial project leader. Expertise in the field of OME including natural history and outcome measure development. Experience leading RCT in primary care in acute sinusitis, and a contributor to other major primary care health service trials in the respiratory field/team member of MRC/DH PEPPER referral study in OME. Lead supervisor of research assistant/PhD student for project.

Håkan Brodin Health economist. Expertise in the field of health technology assessment, especially the area of detailed primary research costing of health-care procedures.

Peter Robb Consultant ENT surgeon with a special interest in OME and paediatric ENT. Secondary care adviser to the project. MRC OME Group clinical investigator for the adjunct risk factor study to TARGET. Secretary of the British Association for Paediatric Otorhinolaryngology.

Mark Haggard Hearing researcher, psychologist and project leader for MRC/DH PEPPER study and for the TARGET trial; and advisor to many journals and public bodies on otitis media (e.g. NICE, Recent Advances, etc.). Expertise in statistical analysis of cohort studies and trials, and in questionnaire development and dissemination.

Paul Little Clinical trialist in health service research. Experience of running large trials in the same field, including factorial trials. Produced relevant trial materials, and principal investigator for trial databases central to this trial, e.g. AOM trials.

Mark Mullee Statistician, will provide statistical advice to the trial, and has advised our group on previous trials of otitis media.

Collaborators

Madge Vickers Head of the MRC GPRF. Considerable experience of running large studies based in primary care and using long-term outcomes. Responsibilities will be to facilitate access to the general practices, advise on the conduct of the trial and oversee the quality control.

Jeanette Martin (left post 3 June 2004) Senior nurse manager for the MRC GPRF at the MRC Clinical trials Unit, London. She has responsibility for the nursing activities within the Framework and her team will be involved in developing nursing training and the standard operating procedures, and managing the quality control for the study.

Team member

Research assistant To be based at Southampton, will have responsibilities for day-to-day overall trial co-ordination (not GPRF fieldwork), production of all trial documentation, liaising with the GPRF

senior nurse, central data collection and entry, quality standards (e.g. tympanometry), producing trial materials, general trouble-shooting, patient interviews and focus groups, randomisation list and protocol coordination and adverse event monitoring. He or she will be expected to help with the data analysis, report writing, papers, and presentations suitable for a PhD.

Company contact

Tamsin Dight Medical affairs manager, Schering-Plough Ltd. Assistance with randomisation, concealment, production and randomisation of active treatments and placebos. Overseeing company provision of trial supplies and holder of confidentiality agreement with University of Southampton. Consultant on company recommendations, e.g. on nasal delivery and help with information sheet.

Expected output of research

The trial team intend to make maximal use of the supporting structures for the trial and broader potential interest groups in dissemination of key research findings. We envisage that this will primarily be in assisting practice teams to manage OME children more effectively, and particularly in the clarification of the role of nasal steroids in improving outcomes and parent satisfaction, and in reducing inappropriate referrals, at a time when demand and referrals are likely to be increasing. We will be introducing feasible technologies into opinion-leading practices with considerable potential to reduce unnecessary diagnostic uncertainties here and efficiently seek out (thus reducing inequities) the appropriate children for the appropriate *remedies*. This trial will also allow development of research capacity through skills transfer on a number of different levels, and thus constitute payback. The data will be presented at national and international meetings, and published in peer-reviewed journals. Copies of the paper will be sent to the MeReC Bulletin and the Drugs and Therapeutics Bulletin. A report will be prepared for the HTA, and a summary of the report sent to magazines that doctors read (e.g. *GP*, *Doctor*, *Pulse*).

Justification of the support requested

We will be using the GPRF with costs over 4 years and 60 practices which include training, travel, consumables and mostly research nurse time. The decision is based on the essential need for a robust and reliable network that can deliver, against the general backdrop of problems with opportunistic recruitment of patients by GPs into research studies.

The trial equipment, namely microtympanometers and audiometers, are absolutely essential for this trial to be recognised at the appropriate level by the scientific establishment – for the standards we are using – and by subsequent Cochrane reviews. The use of mini-tymps with printouts is fully justified on the basis of validity checks and training issues. We are using an established and reliable company, Starkey Laboratories Ltd, based in Stockport, who agreed to a 20% discount for our bulk order of 60 MTP 10 mini-tymps with inbuilt audiometers. We propose that the eventual donation of this equipment to the practices will improve patient satisfaction, the NHS infrastructure in primary care, and also motivation and study compliance through a sense of ownership.

We require a research assistant at the appropriate grade suitable for completion of a PhD, depending on age and previous experience, for 4 years. This post will require someone with management capabilities. Our institution will require 40% on costs.

We require a part-time secretary based at Southampton (Cle 3 [Clerical Assistant Grade 3]) for 1 day per week with the same on costs.

Health economist time also needs to be purchased, given the high level of demand for senior health economists' time and our requirements for 1 day per week for 1 year (distributed over 4 years) plus on costs. We have also included consultancy fees for our statistician.

Stationery, telephone and trial materials are needed for the host institution and are important for our outcome measures.

Computer and software with appropriate statistical packages are needed for the research assistant and our trial database.

We estimate that we need 10 steering meetings at £100 per person for this national trial, and also some reserves for consultancies.

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Appendix A

Trial flow list of procedures

Case identification

GP, HV, Nurse refer case to *R*esearch *N*urse at *1* (sequence point) appointment.

RN uses 'continuous' audit protocol to identify and invite by telephone or post – approximately 3000 invitations in total to at-risk children.

RN1

- Patient/parent attend nurse for otoscopy/ microtympanometry appointment. Trial management of otitis media discussed (10 minutes per patient). Total 1050 bilateral agree to watchful waiting.
- 1050 telephone calls or postcards 1 week before next appointment.

RN2

- 3 months' watchful waiting complete. Otoscopy/microtympanometry. 52% persistent bilateral or 546 cases (10-minute appointment) identified. Local GP and trial fax/telephone hotline support on interpretation of tympanograms.
- 158 not randomised. 28 referred to ENT. 130 refuse consent.
- *388–400 agree to randomisation* (rounded figures and assuming no further dropouts for costings) (+30 minute appointment). Informed consent taken. Randomised in blocks of four.
- Baseline measures in 400.
- Demographic details.

- History including previous 15-month attendance/antibiotic/analgesic consumption.
- PTA.
- Height and weight.
- OM8-30.
- Instructions on trial use of medications.
- Make 1-month appointment with RN.
- At 7 days 400 telephone calls for assistance with questionnaire/diary completion. Check concealment. Use of short form adapted adherence questionnaire.
- Reminder postcard 1 week before appointment due.

RN3

- 1-month outcome measures. 400 (30-minute appointment).
- Medication review adherence, adverse events, check symptom diaries completed, audit analgesic antibiotic use, monitor referral and outcomes.
- Otoscopy/microtympanometry.
- PTA.
- Height, weight.
- Instructions on medication repeated.
- Make 3-month appointment.
- Post baseline and 1-month data and trial medication to Southampton.
- Make second appointment for non-responders. (Up to two further telephone calls and two postcards.)
- Follow-up dropouts with telephone call with reasons.
- Assistance/adherence telephone call at 1 month 1 week. Reminder to attend by postcard before 3 months.

RN4

- 3-month outcome measures in 400 (30-minute appointment).
- Medication review adherence adverse events, check symptom diary, audit analgesic antibiotic use, monitor referral and outcomes.
- OM8-30.
- Otoscopy/microtympanometry.
- PTA.
- Height, weight.
- Instructions on medication.
- Schedule final 9-month appointment.
- Post 3-month data and trial medication to Southampton.
- Make second appointment for non-responders (up to two further telephone calls and two postcards).
- Follow up dropouts with telephone calls with reasons.
- Reminder telephone calls/postcards for RN5 at 9 months.

RN5

- 9-month outcomes in 400 (30-minute appointment).
- Check symptom/events sheet, e.g. time off work, recurrent episodes, antibiotics, analgesics.
- Monitor referral letters, OPD appointments, listed or actual surgery through practice audit.
- OM8-30.
- Otoscopy/microtympanometry.
- PTA.
- Height, weight.
- Exit interview to include treatment preferences.
- Post trial data and final audit data to Southampton.

Appendix 12

First screening

GNOME: First screening

DATE OF APPOINTMENT ……..

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

OTOSCOPY *please circle*:

	Clear	RIGHT	LEFT
If you suspect wax or perforation to be a problem check by using tympanometry (see Appendix 4)	**Wax**	RIGHT	LEFT
	Perforation	RIGHT	LEFT
Exclude child from study ←	**Grommet**	RIGHT	LEFT

TYMPANOMETRY

if **FAIL**, *please circle combination*: B + C2 or B + B

if **PASS**, please tick box indicating patient has been excluded from study and explanation has been given to them as to why ☐

Please tell the parents / guardians that you may invite their child back later or they can bring their child back if they have any ear problems

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

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

Please attach print out

Please turn over

If child has FAILED the tympanometry

CHECK EXCLUSION CRITERIA

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

If yes, your child is not eligible because tympanometry, the main measure of the study, is not valid with grommets

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

If yes, as above

Do you have any concerns about your child's growth? ☐ Yes ☐ No

If yes, your child is not eligible, see your health visitor

Is your child hypersensitive to mometasone (Nasonex)? ☐ Yes ☐ No

If yes, your child is not eligible as trial medication is mometasone

Has your child had systemic steroids in the previous 3 months or do they have poorly controlled asthma? ☐ Yes ☐ No

If yes, your child is not eligible because we don't want to exceed the steroid dose

Has your child had recent epistaxis in the last month? ☐ Yes ☐ No

If yes, your child is not eligible as the spray could make their nose bleed

If none are present, continue

PARENT INFORMED ABOUT NEXT PART OF TRIAL

Give second letter to parent / guardian

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

……

……

……

OPTIONAL

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

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

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

Appendix 13

Health economics forms – revised

GNOME: Costs to parents 1

To be completed when taking BASELINE measures

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

1. SELF-MEDICATION USE FOR EAR PROBLEMS

Over the **past 12 months** have you self-treated your child (without coming to surgery) for an ear problem?

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

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

b) Using a nose spray? ☐ Yes ☐ No

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

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

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

2. CONTACT WITH HEALTHCARE PROVIDERS

a) Has your child been admitted to hospital in the past 12 months?

Yes ☐ No ☐

If yes,

Name of hospital	Name of ward	Reason for admission	Date of admission	Date of discharge

b) Has your child had any operations over the past 12 months? ☐ Yes ☐ No

If yes,

Name of hospital	Type of operation

c) Has your child used any of the following hospital outpatient services over the past 12 months?

a) A&E Yes ☐ No ☐ If yes, total number of attendances ……..….

b) Audiology dept Yes ☐ No ☐ If yes, total number of attendances ……..….

c) ENT Yes ☐ No ☐ If yes, total number of attendances …….

d) Other, please specify …… If yes, total number of attendances ……..

d) Has your child seen any of the following community healthcare professionals over the past 12 months?

Community healthcare professional	*Please tick one box*	Total number of occasions (if applicable)
GP	Yes ☐ No ☐	
Practice nurse	Yes ☐ No ☐	
District nurse	Yes ☐ No ☐	
Health visitor	Yes ☐ No ☐	
Speech therapist	Yes ☐ No ☐	
Hearing therapist	Yes ☐ No ☐	
Other (please specify) ……..	Yes ☐ No ☐	

3. YOUR DETAILS

a) What is the highest grade of school you have completed?

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

b) Which of the following best describes your current marital status?

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

c) Which of the following best describes YOUR CHILD'S racial background?

☐ White ☐ Oriental ☐ Afro-Caribbean

☐ Bangladeshi/Indian ☐ Mixed race ☐ Other group

If mixed race or other group, please specify ……

d) Is English the first language spoken at home?

Yes ☐ No ☐

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

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

☐ Less than £10k ☐ £10k–£20k ☐ £21k–£30k

☐ £31k–£40k ☐ £41k–£50k ☐ Over £50k

GNOME: Costs to parents 2

To be completed when taking 3 MONTH measures

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

1. SELF-MEDICATION USE FOR EAR PROBLEMS

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

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

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

b) Using a nose spray? ☐ Yes ☐ No

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

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

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

2. CONTACT WITH HEALTHCARE PROVIDERS

a) Has your child been admitted to hospital in the past 3 months?

Yes ☐ No ☐

If yes,

Name of hospital	Name of ward	Reason for admission	Date of admission	Date of discharge

Version 2, dated 18 May 2005

b) Has your child had any operations over the past 3 months? ☐ Yes ☐ No

If yes,

Name of hospital	Type of operation

c) Has your child used any of the following hospital outpatient services over the past 3 months?

a) A&E Yes ☐ No ☐ If yes, total number of attendances ……..….

b) Audiology dept Yes ☐ No ☐ If yes, total number of attendances ……..….

c) ENT Yes ☐ No ☐ If yes, total number of attendances …….

d) Other, please specify ……. If yes, total number of attendances …….

d) Has your child seen any of the following community healthcare professionals over the past 3 months?

Community healthcare professional	*Please tick one box*	Total number of occasions (if applicable)
GP	Yes ☐ No ☐	
Practice nurse	Yes ☐ No ☐	
District nurse	Yes ☐ No ☐	
Health visitor	Yes ☐ No ☐	
Speech therapist	Yes ☐ No ☐	
Hearing therapist	Yes ☐ No ☐	
Other (please specify) ……..	Yes ☐ No ☐	

GNOME: Costs to parents 3

To be completed when taking 9 MONTH measures

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

1. SELF-MEDICATION USE FOR EAR PROBLEMS

Over the **past 6 months** have you self-treated your child (without coming to surgery) for an ear problem?

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

If YES, How many occasions? ☐ 0–1 ☐ 1–2 ☐ 2–4 ☐ More than 4

b) Using a nose spray? ☐ Yes ☐ No

If YES, How many occasions? ☐ 0–1 ☐ 1–2 ☐ 2–4 ☐ More than 4

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

If YES, How many occasions? ☐ 0–1 ☐ 1–2 ☐ 2–4 ☐ More than 4

2. CONTACT WITH HEALTHCARE PROVIDERS

a) Has your child been admitted to hospital in the past 6 months?

Yes ☐ No ☐

If yes,

Name of hospital	Name of ward	Reason for admission	Date of admission	Date of discharge

Version 1, dated 18 May 2005

b) Has your child had any operations over the past 6 months? ☐ Yes ☐ No

If yes,

Name of hospital	Type of operation

c) Has your child used any of the following hospital outpatient services over the past 6 months?

a) A&E Yes ☐ No ☐ If yes, total number of attendances ……..…

b) Audiology dept Yes ☐ No ☐ If yes, total number of attendances ……..…

c) ENT Yes ☐ No ☐ If yes, total number of attendances ……

d) Other, please specify …… If yes, total number of attendances ……..…

d) Has your child seen any of the following community healthcare professionals over the past 6 months?

Community healthcare professional	*Please tick one box*	Total number of occasions (if applicable)
GP	Yes ☐ No ☐	
Practice nurse	Yes ☐ No ☐	
District nurse	Yes ☐ No ☐	
Health visitor	Yes ☐ No ☐	
Speech therapist	Yes ☐ No ☐	
Hearing therapist	Yes ☐ No ☐	
Other (please specify) ……..	Yes ☐ No ☐	

GNOME: Health Economic Evaluation Form 1

To be completed at time of taking BASELINE MEASURES by computer search

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

In the previous 12 months

1. All appointments

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

2. Treatment courses for OM or OME (ear problems)

a) Antibiotics:

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

b) Autoinflation Yes / No

if yes, date …… no. of times per day …… total duration of treatment ……

c) Decongestants and antihistamines:

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

d) Analgesics:

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Prescribed medication for other reasons

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

Date …….. name …… dose …….. days ……..…

3. Any investigations in their records

e.g. blood tests / X-rays,

Please state what …… Date: …… Number ……

Please state what …… Date: …… Number ……

Please state what …… Date: …… Number ……

4. Outpatient hospital referrals

Date ……

Main reason ……

……

To where?

☐ ENT ☐ Audiology

☐ Other please state ……..

Date ……

Main reason ……

……

To where?

☐ ENT ☐ Audiology

☐ Other please state ……..…..

Date ……
Main reason ……
……
To where?

☐ ENT ☐ Audiology
☐ Other please state ……...

Date ……
Main reason ……
……
To where?

☐ ENT ☐ Audiology
☐ Other please state ……

5. Referral for speech therapy

Date ……
main reason ……
……..
to where? ……

Date ……
main reason ……
……..
to where? ……

6. Referral to community healthcare professional (e.g. community paediatrician)

Date ……
Main reason ……
……..
To where? ……

Date ……
Main reason ……
……..
To where? ……

Date ……
Main reason ……
……..
To where? ……

Date ……
Main reason ……
……..
To where? ……

7. Hospitalisation

Was the child admitted to hospital for:

a) Grommets / t-tubes / ventilation tubes: Yes / No
b) Adenoidectomy: planned Yes / No
done Yes / No
c) Other reason Yes / No
If yes, please state ……

If yes to a) or b) or c) please state:

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

GNOME: Health Economic Evaluation Form 2

To be completed at time of taking 9 MONTH MEASURES by computer search

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

In the previous 9 months

1. All appointments

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

Please turn over

2. Treatment courses for OM or OME (ear problems)

a) Antibiotics:

Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..

b) Autoinflation Yes / No

If yes, date …… no. of times per day ……. total duration of treatment ……

c) Decongestants and antihistamines:

Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..

d) Analgesics:

Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..

Prescribed medication for other reasons

Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..
Date …….. name …….. dose …….. days ……..

3. Any Investigations in their records

e.g. blood tests / X-rays,

Please state what …… Date: …… Number ……
Please state what …… Date: …… Number ……
Please state what …… Date: …… Number ……

4. Outpatient hospital referrals

Date ……
Main reason ……
……
To where?

☐ ENT ☐ Audiology
☐ Other please state ……..

Date ……
Main reason ……
……
To where?

☐ ENT ☐ Audiology
☐ Other please state ……..

Date ……
Main reason ……
……
To where?

☐ ENT ☐ Audiology
☐ Other please state ……...

Date ……
Main reason ……
……
To where?

☐ ENT ☐ Audiology
☐ Other please state ……...

5. Referral for speech therapy

Date ……
Main reason ……
……..
To where? ……

Date ……
Main reason ……
……..
To where? ……

6. Referral to community healthcare professional (e.g. community paediatrician)

Date ……
Main reason ……
……..
To where? ……

Date ……
Main reason ……
……..
To where? ……

Date ……
Main reason ……
……..
To where? ……

Date ……
Main reason ……
……..
To where? ……

7. Hospitalisation

Was the child admitted to hospital for:

a) Grommets / t-tubes / ventilation tubes: Yes / No
b) Adenoidectomy: planned Yes / No
done Yes / No
c) Other reason Yes / No
If yes, please state ……

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

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

GNOME study

Your health today

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

Version 2, dated 18/4/05

Parents / guardians

Please can you complete this questionnaire for your child. Where possible please ask your child the questions and get their response. We realise that for very young children this may be difficult but please do the best you can.

Section 1: Describing your child's health TODAY

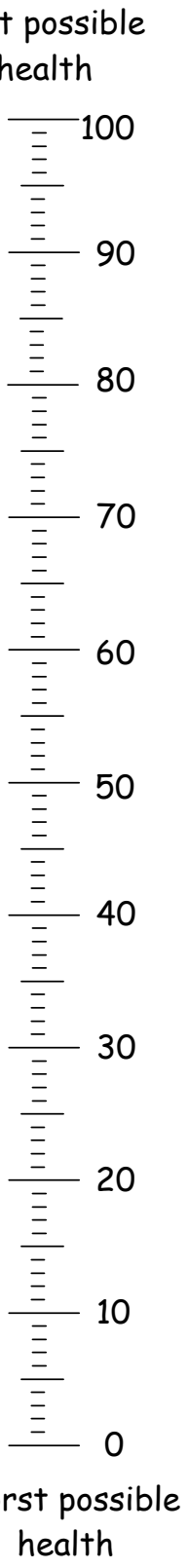
Please tick ONE box in each section which best describes your child's health TODAY

Mobility	
Your child has no problems walking about	❑ 1
	❑ 2
Your child has some problems walking about	❑ 3
	❑ 4
Your child had a lot of problems walking about	❑ 5
Self-care	
Your child has no problems washing or dressing himself/herself	❑ 1
	❑ 2
Your child has some problems washing or dressing himself/herself	❑ 3
	❑ 4
Your child is unable to wash or dress himself/herself	❑ 5
Usual activities (e.g. going to school, hobbies, sports, playing)	
Your child has no problems with performing his/her usual activities	❑ 1
	❑ 2
Your child has some problems with performing his/her usual activities	❑ 3
	❑ 4
Your child is unable to perform his/her usual activities	❑ 5
Pain / discomfort	
Your child has no pain or discomfort	❑ 1
	❑ 2
Your child has moderate pain or discomfort	❑ 3
	❑ 4
Your child has extreme pain or discomfort	❑ 5
Feeling worried, sad or unhappy	
Your child is not worried, sad or unhappy	❑ 1
	❑ 2
Your child is moderately worried, sad or unhappy	❑ 3
	❑ 4
Your child is extremely worried, sad or unhappy	❑ 5

Section 2: How good is your child's health TODAY

- Please indicate on this scale how good or bad your child's health is today.
- The best possible health you can imagine is marked 100.
- The worst possible health you can imagine is marked 0.
- Please draw a line from the box below to the point on the scale that indicates how good or bad your child's health is today.

Your child's health today



Section 3: About your child's health in general

Please tick **ONE** box for each question

1. During the last 12 months how has your child's health been in general? Would you say it has been:

Very good ❑ Good ❑ Fair ❑ Poor ❑ Very poor ❑

2. During the last 2 weeks has your child had to cut down on any of the things they usually do (for example at school) because of illness or injury?

Yes ❑ No ❑

3. During the last month has your child had any health problems that they needed to see their doctor or practice nurse about?

Yes ❑ No ❑

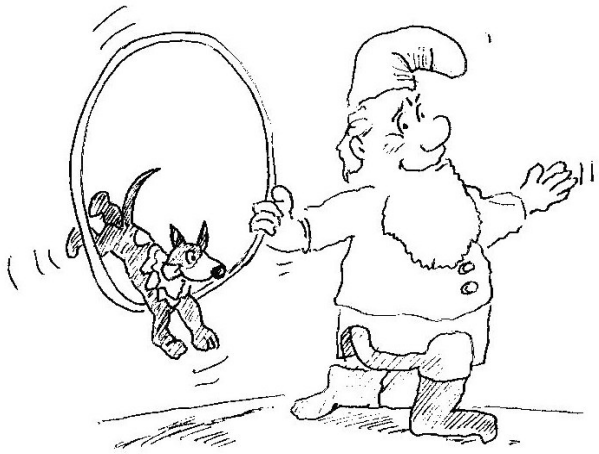
4. Does your child have any of these conditions?

Asthma	Yes ❑	No ❑
Eczema	Yes ❑	No ❑
Hay fever	Yes ❑	No ❑
Diabetes	Yes ❑	No ❑

Thank you for helping us

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

GNOME Study



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

Date questionnaire completed ……

Version 1, dated 18 May 2005

Permission has been given for the use of this document in the GNOME Study and was obtained from:

Health Utilities Inc. (HUInc)
88 Sydenham Street
Dundas ON, Canada L9H 2V3
Tel (905) 525-9140, ext 22389 / 22377
Fax (905) 627-7914
http://www.healthutilities.com

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

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

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

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

5. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to be understood when speaking his/her own language with people who do not know them?
   a. Able to be understood completely
   b. Able to be understood partially
   c. Unable to be understood
   d. Unable to speak at all

6. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to be understood when speaking with people who know them well?
   a. Able to be understood completely
   b. Able to be understood partially
   c. Unable to be understood
   d. Unable to speak at all

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

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

9. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to walk? Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.
   a. Able to walk around the neighbourhood without difficulty, and without walking equipment
   b. Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person
   c. Able to walk around the neighbourhood with walking equipment, but without the help of another person
   d. Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood
   e. Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood
   f. Unable to walk at all

10. Which **ONE** of the following best describes your child's ability, during the past 4 weeks, to use his/her hands and fingers? Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands and fingers.
    a. Full use of two hands and ten fingers
    b. Limitations in the use of hands or fingers, but does not require special tools or the help of another person
    c. Limitations in the use of hands or fingers, independent with use of special tools (does not require the help of another person)
    d. Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools)
    e. Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools)
    f. Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools)

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

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

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

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

15. Which **ONE** of the following best describes the pain or discomfort your child has experienced during the past 4 weeks?
    a. Free of pain and discomfort
    b. Occasional pain or discomfort. Discomfort relieved by non-prescription medication or self-control activity without disruption of normal activities
    c. Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities
    d. Frequent pain or discomfort; frequent disruption of normal activities. Discomfort requires prescription medication for relief
    e. Severe pain or discomfort. Pain not relieved by medication and constantly disrupts normal activities

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

    a. Excellent

    b. Very good

    c. Good

    d. Fair

    e. Poor

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

    a. Person recording the answers on the form

    b. Child

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

        1. ……

        2. ……

        3. ……

        4. ……

18. Who recorded the answers on this questionnaire form?

    a. Parent of the child

    b. Other (please specify) ……

Many thanks for all your help

Appendix 14

Unit costs

Unit costs of resource items (pound sterling, 2006–7 prices)

Resource item (unit)	Unit cost (£)	Unit cost range[a] (£)	Source of unit cost
Hospital outpatient services			
A&E (attendance)	79.71	69–90	NHS Reference Costs (2006)[85]
Audiology (contact hour)	66.00	23–46	NHS Reference Costs (2006)[85]
Consultant psychiatrist (per hour of client contact)	246.00		Netten and Curtis (2006)[84]
Dental	92.61	64–169	NHS Reference Costs (2006)[85]
Dermatology	117.46	84–133	NHS Reference Costs (2006)[85]
Dietitian (per hour of client contact)	31.00		Netten and Curtis (2006)[84]
ENT (attendance)	116.97	89–139	NHS Reference Costs (2006)[85]
Nephrologist	242.47	147–258	NHS Reference Costs (2006)[85]
Ophthalmology	105.59	79–127	NHS Reference Costs (2006)[85]
Orthopaedic	99.19	74–112	NHS Reference Costs (2006)[85]
Orthoptic	52.32	38–75	NHS Reference Costs (2006)[85]
Orthoptic clinic	52.32	38–75	NHS Reference Costs (2006)[85]
Paediatrician	228.96	178–282	NHS Reference Costs (2006)[85]
Paediatric cardiology	240.18	133–298	NHS Reference Costs (2006)[85]
Paediatric physiotherapist	57.65	34–57	NHS Reference Costs (2006)[85]
Paediatric surgeon	175.33	117–223	NHS Reference Costs (2006)[85]
Radiographer (per hour of client contact)	43.00		Netten and Curtis (2006)[84]
Senior house officer (per hour on duty)	47.00		Netten and Curtis (2006)[84]
Speech and language therapist (per hour of client contact)	40.00		Netten and Curtis (2006)[84]
Surgery	175.33	117–223	NHS Reference Costs (2006)[85]
Surgery (follow-up)	84.98	48–87	NHS Reference Costs (2006)[85]
Surgery (oral)	141.54	97–167	NHS Reference Costs (2006)[85]
Urology	157.52	111–184	NHS Reference Costs (2006)[85]
Walk-in centre	29.29	22–40	NHS Reference Costs (2006)[85]
Hospital inpatient admissions			
Adenoidectomy	1206.58	618.84–1397.68	NHS Reference Costs (2006)[85]
Allergic reaction	604.27	357.76–747.5125	NHS Reference Costs (2006)[85]
Asthma	696.30	442.415–810.245	NHS Reference Costs (2006)[85]
Asthma attack	696.30	442.415–810.245	NHS Reference Costs (2006)[85]
Broken arm	1085.54	426.45–1021.265	NHS Reference Costs (2006)[85]
Broken wrist	1085.54	426.45–1021.265	NHS Reference Costs (2006)[85]
Chest pain	458.49	408.845–848.0375	NHS Reference Costs (2006)[85]

continued

Unit costs of resource items (pound sterling, 2006–7 prices) (continued)

Resource item (unit)	Unit cost (£)	Unit cost range[a] (£)	Source of unit cost
Circumcision	1154.52	696.28–1317.3175	NHS Reference Costs (2006)[85]
Circumcision	1154.52	696.28–1317.3175	NHS Reference Costs (2006)[85]
Dental treatment	1000.87	676.99–1291.51	NHS Reference Costs (2006)[85]
Ear infection	1034.91	665.1–1303.835	NHS Reference Costs (2006)[85]
Ear wash	1034.91	665.1–1303.835	NHS Reference Costs (2006)[85]
Excision of lesion of eyelid	979.56	654.4625–1355.725	NHS Reference Costs (2006)[85]
Excision of lesion of tongue	1206.58	618.84–1397.68	NHS Reference Costs (2006)[85]
Fall	1544.03	426.45–1021.265	NHS Reference Costs (2006)[85]
Fracture	1085.54	426.45–1021.265	NHS Reference Costs (2006)[85]
Greenstick fracture left distal radius and ulna	1624.25	641.68–1683.135	NHS Reference Costs (2006)[85]
Grommets	1034.91	665.1–1303.835	NHS Reference Costs (2006)[85]
Hernia repair	2067.01	1472.61–2409.71	NHS Reference Costs (2006)[85]
Inguinal hernia repair	1700.65	1216.54–1993.86	NHS Reference Costs (2006)[85]
Lump removal on side of tongue	1206.58	618.84–1397.68	NHS Reference Costs (2006)[85]
Myringoplasty	2997.20	1326–3472	NHS Reference Costs (2006)[85]
Myringotomy	1034.91	665.1–1303.835	NHS Reference Costs (2006)[85]
Nausea and vomiting	739.67	467.99–956.1975	NHS Reference Costs (2006)[85]
Observation of neurological status after a fall	1085.54	426.45–1021.265	NHS Reference Costs (2006)[85]
Otalgia (earache)	694.37	432.9275–906.56	NHS Reference Costs (2006)[85]
Perichondritis of the ear	819.98	498.02–1078.52	NHS Reference Costs (2006)[85]
Pinnaplasty	1200.59	685.48–1645.005	NHS Reference Costs (2006)[85]
Rash	751.72	474.945–1184.51	NHS Reference Costs (2006)[85]
Removal of foreign body from nose	1006.25	642.0875–1221.65	NHS Reference Costs (2006)[85]
Swelling of face and eyes	751.72	474.945–1184.51	NHS Reference Costs (2006)[85]
Tonsil and adenoid removal	2738.15	1974.16–5695.227	NHS Reference Costs (2006)[85]
Tonsillectomy	1531.57	1974.16–5695.227	NHS Reference Costs (2006)[85]
Tooth extractions	1206.58	618.84–1397.68	NHS Reference Costs (2006)[85]
Umbilica hernia	1700.65	1216.54–1993.86	NHS Reference Costs (2006)[85]
Investigative tests			
Erythrocyte sedimentation rate test	2.78	2.58–4.43	NHS Reference Costs (2006)[85]
Full blood count	2.78	2.58–4.43	NHS Reference Costs (2006)[85]
Mid-stream specimen of urine test	1.45	1.0375–2.27	NHS Reference Costs (2006)[85]
Throat swab	6.86	5.59–9.8	NHS Reference Costs (2006)[85]
Thyroid-stimulating hormone test	1.45	1.0375–2.27	NHS Reference Costs (2006)[85]
Tympanogram	18.81		Primary research
X-ray	19.22	15.185–22.7575	NHS Reference Costs (2006)[85]
Community services			
Adolescent psychiatrist	362.05	304–416	NHS Reference Costs (2006)[85]
Community psychiatric nurse (per hour of client contact)	78.81		Netten and Curtis (2006)[84]
Dentist	58.46	42–90	NHS Reference Costs (2006)[85]

Unit costs of resource items (pound sterling, 2006–7 prices) (continued)

Resource item (unit)	Unit cost (£)	Unit cost range[a] (£)	Source of unit cost
District nurse (per home visit)	23.00		Netten and Curtis (2006)[84]
GP – home visits (per visit lasting 13.2 minutes + 12 minutes' travelling)	69.00		Netten and Curtis (2006)[84]
GP – out of hours consultation	69.00		Netten and Curtis (2006)[84]
GP – telephone consultation	27.00		Netten and Curtis (2006)[84]
GP – surgery consultation lasting 12.6 minutes	31.00		Netten and Curtis (2006)[84]
Health visitor (per home visit)	35.00		Netten and Curtis (2006)[84]
Health visitor (per hour of client contact)	84.00		Netten and Curtis (2006)[84]
Hearing therapist	65.75	42–81	NHS Reference Costs (2006)[85]
Homeopath	135.00		Local provider
Occupational therapist (per hour of client contact)	40.00		Netten and Curtis (2006)[84]
Ophthalmologist	105.59	79–127	NHS Reference Costs (2006)[85]
Optometrist	105.59	79–127	NHS Reference Costs (2006)[85]
Orthoptic	52.32	38–75	NHS Reference Costs (2006)[85]
Out of hour service (SEBDOC)	69.00		Netten and Curtis (2006)[84]
Paediatrician	238.94	210–388	NHS Reference Costs (2006)[85]
Physiotherapist	40.00		Netten and Curtis (2006)[84]
Practice nurse	29.00		Netten and Curtis (2006)[84]
Practice nurse (per hour of client contact)	29.00		Netten and Curtis (2006)[84]
Practice nurse (per telephone consultation)	10.00		Netten and Curtis (2006)[84]
School nurse	33.74	26–56	NHS Reference Costs (2006)[85]
Speech therapist (per hour of client contact)	40.00		Netten and Curtis (2006)[84]
Urologist	157.52	111–184	NHS Reference Costs (2006)[85]
Walk-in centre	29.29	22–40	NHS Reference Costs (2006)[85]
Medication			
Aciclovir	3.07		PCA[122] – data by individual preparation
Aciclovir suspension	36.62		PCA[122] – data by individual preparation
Adcortyl orabase paste	1.26		PCA[122] – data by individual preparation
Alimemazine	6.42		PCA[122] – totals by chemical entities
Amoxicillin	1.90		PCA[122] – totals by chemical entities
Aqueous cream	2.91		BNF 54[86]
Auto inflation	4.46		PCA[122] – data by individual preparation
Balneum bath oil	5.38		BNF 54[86]
Balneum plus	17.32		BNF 54[86]
Beclometasone	14.99		BNF 54[86]
Beclometasone inhaler	4.89		BNF 54[86]
Becotide 50	12.27		PCA[122] – totals by chemical entities

continued

Unit costs of resource items (pound sterling, 2006–7 prices) (continued)

Resource item (unit)	Unit cost (£)	Unit cost range[a] (£)	Source of unit cost
Begrivac	5.03		PCA[122] – data by individual preparation
Betamethasone valerate cream 0.025%	3.64		PCA[122] – data by individual preparation
Betnesol	2.89		PCA[122] – data by individual preparation
Brufen (elixir)	3.52		PCA[122] – totals by chemical entities
Galenphol	0.40		PCA[122] – data by individual preparation
Calpol	2.90		PCA[122] – totals by chemical entities
Canesten 1%	2.88		PCA[122] – data by individual preparation
Cefaclor	8.34		PCA[122] – totals by chemical entities
Cefalexin	3.65		PCA[122] – totals by chemical entities
Ceporex syrup	1.56		PCA[122] – data by individual preparation
Cetirizine	2.56		PCA[122] – totals by chemical entities
Cetraben emollient	5.61		BNF 54[86]
Chloramphenicol eye drops	1.77		PCA[122] – data by individual preparation
Chloramphenicol eye ointment	2.78		PCA[122] – data by individual preparation
Chlorphenamine oral solution	2.43		PCA[122] – totals by chemical entities
Clobetasone butyrate	3.64		PCA[122] – totals by chemical entities
Clarithromycin	13.07		PCA[122] – totals by chemical entities
Clotrimazole cream	5.07		PCA[122] – totals by chemical entities
Co-Amoxiclav (Amoxicillin/Clavul Acid)	7.60		PCA[122] – totals by chemical entities
Daktarin 2%	2.30		PCA[122] – totals by chemical entities
Dermol 500 lotion	6.97		PCA[122] – data by individual preparation
Dimotane	1.91		PCA[122] – totals by chemical entities
Dimotane plus	0.77		PCA[122] – data by individual preparation
Diprobase	6.76		BNF 54[86]
Diprobase ointment	1.34		BNF 54[86]
Doublebase gel	2.77		BNF 54[86]
E45 cream	6.20		BNF 54[86]
Enzira	6.59		BNF 54[86]
Ephedrine hydrochloride	1.44		PCA[122] – totals by chemical entities
Epipen	57.90		PCA[122] – data by individual preparation
Erythromycin	4.52		PCA[122] – totals by chemical entities
Erythromycin	5.80		PCA[122] – totals by chemical entities
Flixonase	51.89		PCA[122] – totals by chemical entities
Flucloxacillin sodium	5.75		PCA[122] – totals by chemical entities
Fluticasone	13.90		PCA[122] – totals by chemical entities
Fluvac	3.98		BNF 54[86]
Fucidic acid cream	2.74		PCA[122] – data by individual preparation
Fucidin H ointment	3.87		PCA[122] – data by individual preparation
Fucithalmic eye drops	2.19		PCA[122] – data by individual preparation
Fusidic acid + hydrocortisone	8.79		PCA[122] – data by individual preparation
Gentamicin ear drops	1.97		PCA[122] – data by individual preparation
Gentisone ear drops	3.82		PCA[122] – data by individual preparation

Unit costs of resource items (pound sterling, 2006–7 prices) (continued)

Resource item (unit)	Unit cost (£)	Unit cost range[a] (£)	Source of unit cost
Glycerol suppositories	0.97		PCA[122] – data by individual preparation
Hydrocortisone cream	6.05		PCA[122] – data by individual preparation
Hydrocortisone	3.80		PCA[122] – data by individual preparation
Hydrocortisone cream	19.15		PCA[122] – data by individual preparation
Hydrocortisone cream	4.30		PCA[122] – data by individual preparation
Hydrocortisone ointment	4.47		PCA[122] – data by individual preparation
Hypromellose	3.32		PCA[122] – totals by chemical entities
Ibuprofen	3.52		PCA[122] – totals by chemical entities
Ibuprofen	4.27		PCA[122] – data by individual preparation
Influenza vaccine	3.98		BNF 54[86]
Junifen	5.21		PCA[122] – totals by chemical entities
Lactulose solution	3.82		PCA[122] – totals by chemical entities
Levocetirizine	8.89		PCA[122] – totals by chemical entities
Locuten-vioform ear drops	1.54		PCA[122] – totals by chemical entities
Loratadine	3.10		PCA[122] – totals by chemical entities
Malathion aqueous lotion	5.32		PCA[122] – totals by chemical entities
Mebendazole	1.44		PCA[122] – totals by chemical entities
Melatonin M/R	28.55		PCA[122] – data by individual preparation
Metronidazole 200 mg 100 ml	10.01		PCA[122] – data by individual preparation
Mometasone furoate 50 (active study drug)	7.83		BNF 54[86]
Mupirocin cream	5.11		PCA[122] – data by individual preparation
Naseptin cream	1.65		PCA[122] – data by individual preparation
Nasonex	8.71		PCA[122] – totals by chemical entities
Nurofen	5.21		PCA[122] – totals by chemical entities
Ofloxacin ophthalmic solution	2.52		PCA[122] – totals by chemical entities
Oilatum bath emollient	5.50		PCA[122] – data by individual preparation
Oilatum plus bath emollient	8.24		PCA[122] – data by individual preparation
Olive oil liquid	0.25		PCA[122] – data by individual preparation
Otex	2.90		PCA[122] – data by individual preparation
Otomize spray	4.50		PCA[122] – data by individual preparation
Otosporin	3.03		PCA[122] – totals by chemical entities
Oxybutynin	12.79		PCA[122] – totals by chemical entities
Paracetamol	2.90		PCA[122] – totals by chemical entities
Penicillin	2.46		PCA[122] – totals by chemical entities
Penicillin V	3.60		PCA[122] – totals by chemical entities
Pholcodine linctus	0.99		PCA[122] – data by individual preparation
Piriton	2.43		PCA[122] – totals by chemical entities
Prednisolone	2.79		PCA[122] – totals by chemical entities
Promethazine hydrochloride	1.94		PCA[122] – totals by chemical entities
Pseudophedrine	1.91		PCA[122] – totals by chemical entities

continued

Unit costs of resource items (pound sterling, 2006–7 prices) (continued)

Resource item (unit)	Unit cost (£)	Unit cost range[a] (£)	Source of unit cost
Salactol	1.88		PCA[122] – data by individual preparation
Salatac gel	3.43		PCA[122] – data by individual preparation
Salbutamol inhaler	3.37		PCA[122] – data by individual preparation
Salbutamol	6.08		PCA[122] – data by individual preparation
Salbutamol inhaler	4.23		PCA[122] – data by individual preparation
Salbutamol syrup	2.08		PCA[122] – data by individual preparation
Salicylic acid paint	1.88		PCA[122] – data by individual preparation
Salicylic acid ointment 50%	81.01		PCA[122] – data by individual preparation
Salmeterol inhaler	38.19		PCA[122] – totals by chemical entities
Seretide 50 evohaler	23.57		PCA[122] – data by individual preparation
Serevent	37.91		PCA[122] – data by individual preparation
Simple linctus	0.42		PCA[122] – data by individual preparation
Simple pediatric linctus	0.30		PCA[122] – data by individual preparation
Sodium bicarbonate ear drops	1.32		PCA[122] – data by individual preparation
Sodium cromoglicate	110.31		PCA[122] – totals by chemical entities
Sodium fusidate	49.15		PCA[122] – totals by chemical entities
Timodine	2.75		PCA[122] – data by individual preparation
Triamcinolone acetonide oral paste 0.1%	1.26		PCA[122] – data by individual preparation
Trimethoprim	1.39		PCA[122] – totals by chemical entities
Typhim VI vaccine	9.49		PCA[122] – data by individual preparation
Urea hydrogen peroxide	2.51		PCA[122] – totals by chemical entities
VAQTA vaccine	15.64		PCA[122] – data by individual preparation
Vermox suspension	1.81		PCA[122] – data by individual preparation
Xylometazoline nasal spray	1.91		PCA[122] – totals by chemical entities

a Ranges for unit costs are specified when unit costs varied according to location or intensity of care.
PCA, *Prescription Cost Analysis: England, 2006*.[122] Based on the *British National Formulary*.[86]

Appendix 15

Mapping analyses to estimate utilities based on responses to the OM8-30 questionnaire

Introduction

Requirement for a mapping algorithm for OM8-30 onto multiattribute utility instruments

Utility measures were not introduced into the GNOME study until the protocol amendment that occurred after approximately one-third of children had finished treatment. Additionally, 21% (279/1305) of utility questionnaires sent to patients recruited after the protocol amendment were not fully completed. However, a generic health-related QoL measure, the OM8-30, was used throughout the trial and was fully completed by approximately 62.5% of parents at each time point (OM8-30 domain scores were available at 407/651 potential patient observations). It was proposed that the OM8-30 questionnaire may include a useful measure that could be used to impute values for the missing utility data.

OM8-30 questionnaire

The OM8-30 instrument contains 32 questions, each with between two and seven levels.[109–111] These are grouped into nine facets that fall into two domains: the PHYS domain contains four facets (global health, ear infections, sleep and respiratory symptoms); the DEV domain contains a further four facets (schooling concerns, speech/language, behaviour and parent QoL); while the ninth facet, RHD, is considered separately from either domain (see *Table 3*, Chapter 2).

The methods used to scale responses from the OM8-30 and calculate domain and facet scores have been described previously, but are briefly summarised here.[110] Each level of response to any given question was assigned particular values that were calculated by initially scaling items dichotomously nearest the median, then conducting categorical regression, and regressing the item categories onto the raw total count for each individual based on baseline data from 441 patients participating in the TARGET trial.[112–114] For all questions (and for facet and domain scores), lower values indicate more problems with the symptom in question. For example, within the global health question, a rating of health as 'very good' is defined as zero, a rating of 'good' equates to a score of 1.25, 'fair' equates to 2.65 and 'poor' equates to 3.69. The spacings for each question were then given a weighting calculated by principal components' analysis of data from the same sample of TARGET trial participants.[110,115] The weighted item scores are then summated to produce scores for the nine facets. The facets are in turn summated based on a further principal components analysis to produce scores for two main domains (DEV and PHYS). The RHD facet is not included within either domain so that it can be used in bias adjustment alongside its objective counterpart, HL. Given that many parents over- or underestimate their child's hearing difficulties, RHD does not correlate perfectly with HL due to (a) an expectancy bias (similar to the placebo effect) and (b) a systematic degree of pessimism/optimism that is observed across the domains and facets of the questionnaire.

Objectives

This study set out to produce regression equations that predict utilities (derived from the HUI2/3 and EQ-5D$_5$ multiattribute utility measures) based on demographic characteristics and responses/scores for the OM8-30 questionnaire using the data from the GNOME study.

Methods

Regression analyses were conducted using STATA Version 10.0 (Stata Corporation, College Station, TX, USA) to identify the statistical model that produced the best estimates of children's utility based on responses and/or scores to the OM8-30 questionnaire and key demographic data.

The dependent variable in the regression analyses comprised children's disutility (one minus the utility). The initial set of models, which investigated alternative functional forms for the mapping model, used HUI3 disutility as the dependent variable, although analyses on the best performing models were also repeated for HUI2 and EQ-5D$_5$ disutility measures. Disutilities were not transformed in any way in order to estimate predicted values on a natural scale. Independent

variables included scores and/or responses on the OM8-30 questionnaire, HL and demographic characteristics.

The data set used to produce the mapping algorithm comprised children from the GNOME trial population for whom the OM8-30 questionnaire and the relevant utility instrument had been completed at the same time point. The GNOME study population was divided into two parts: 75% of children were randomly assigned to the 'estimation sample', which was used in the regression to generate the mapping model and coefficients, while the remaining 25% of children (assigned to the 'validation sample') were not used to estimate the model and were instead used to test the performance of the algorithm (patients were allocated to the different data sets using the RAND function in Microsoft EXCEL). No validation sample was used for sensitivity analyses specific to data from individual time points, as such analyses typically included only 80–100 child observations.

As HL was not directly measured within the trial, objective measures of HL were predicted based on tympanometric measurements, adjusted for children's age, based on an ACET model derived from a large database of 3085 children aged between 3.25 and 6.75 years who were screened for the TARGET trial.[116]

Analyses were conducted in a sequential fashion over five main stages:

1. The first stage aimed to identify the appropriate level(s) of OM8-30 responses/scores to include in the mapping algorithm (i.e. responses/scores for individual questions, versus facet scores, versus domain scores).
2. The second stage aimed to identify the most appropriate functional form for the model. The functions investigated included:
   i. OLS.
   ii. OLS with suppressed constant: as disutilities are bounded at zero (perfect health) and as most of the OM8-30 questions, facets and domain scores code 'no problems' as zero, it was hypothesised that the constant in the mapping model would be approximately zero. Furthermore, constraining the constant term to equal zero frees one degree of freedom. The 'noconstant' option within STATA was therefore investigated to assess if it improved the accuracy of predictions.
   iii. Generalised linear models (GLM) using gamma or log-normal distributional families. These models were investigated, as disutility data are frequently positively skewed and cannot take negative values. Within STATA, these functions were modelled using the gamma family of distributions with an identity link function or using Gaussian distributions with logarithmic link functions.
   iv. Two-part models: in addition to one-part models that directly predicted disutility on a continuous scale, several two-part models were also investigated as 36% (128/352) of HUI3 utility questionnaires from the trial showed children to have a disutility of zero (perfect health). The two-part models first used logistic regression to predict the probability that each child would have perfect health at each time point. Following estimation of these models, separate regressions were conducted using OLS or GLM to predict disutility for the subset of child-observations for which disutility did not equal zero. To produce predictions for two-part models, all child observations with a greater than 50% probability of having perfect health were assumed to have a predicted utility of one, while the utility of the remaining observations was based on the disutility predicted from the second model.
3. The third stage comprised evaluation of whether or not the inclusion of demographic variables (namely age and sex) within the model improved the accuracy of predictions. Age was rounded to the nearest month and was assumed to increase during the trial.
4. The fourth stage comprised assessment of the performance of the final model of HUI3 disutility.
5. The fifth and final stage comprised applying the model specifications that performed best for HUI3 to data on disutilities measured using HUI2 and EQ-$5D_5$.

At each stage, a number of different models were investigated, with a small number of models being selected for further investigation based on the accuracy of the predictions generated. Predictions of each child's disutility and estimates of the standard errors around such predictions were generated for each model using the predict function in STATA; the predicted disutilities were converted back into utilities and any utilities

predicted to be greater than one were assumed to equal one. The absolute error (i.e. the absolute difference between predicted and observed utility) was calculated for each observation and was used to calculate the MAE and the proportion of cases for which predictions deviated from the observed values by more than 0.1, 0.25 or 0.5. The MSE (average of the squared absolute errors for each observation) was also calculated. Final decisions about the best functional form and which variables should be included in the model were primarily based on the MAE for the validation sample (MAE_{Val}) and the degree of bias/plausibility of the predicted disutilities. For each model, measures of goodness of fit [adjusted r^2, root MSE, Akaike/Bayesian information criterion (AIC/BIC) and pseudo r^2 for logistic models] were also recorded. Coefficients with implausible signs (i.e. those suggesting that fewer symptoms on an OM8-30 facet/domain correlated with lower QoL) were noted as they may indicate overfitting or a lack of reliability.

Disutilities and OM8-30 responses/scores relating to the same child at different time points were linked using the cluster command that comprises an option for regression analyses within STATA.[117] Clustering by patient allows for the fact that repeated observations of the same child are related, and ensures that standard errors are based on the actual number of independent observations within the data set. Within clustered analyses, all standard errors are calculated using the robust method; this method does not assume the specified model is true or that errors are normally distributed and homoskedastic.[117,118]

Analyses using responses from individual OM8-30 questions were conducted using backwards stepwise regression to identify the parameters having most influence on disutility. The threshold for exclusion from the model (pr) was 0.2 and the threshold for reinclusion into the model (pe) was 0.19. The parameters that were selected by stepwise regression were included within a separate non-stepwise regression that was used for estimation of coefficients and generation of predictions.

Results

Stage 1: Investigations into the optimal level of OM8-30 scores for use in the models

The first analyses were conducted using the responses or scores for individual questions on the OM8-30 questionnaire as independent variables, treating data from all time points as independent observations. Although it was anticipated prior to commencing analyses that the data set would not be sufficiently large to reliably estimate models that used all OM8-30 item scores, these models were nonetheless generated to investigate their properties.

It was hypothesised that the global health question (in which parents rate their child's health as very good, good, fair or poor) was likely to correlate highly with children's disutility; this question was therefore captured within three dummy variables representing parents' actual responses, rather than using weighted scores. Responses to this question alone were found to explain 41% of variability in HUI3 disutilities. As there are 30 questions within the OM8-30 and there were only around 264 child observations for which full OM8-30 and HUI3 data were available, it was not possible to include all levels of all questions as dummy variables within the regression. Furthermore, the relatively small study data set is unlikely to be sufficient to accurately estimate coefficients for 30–100 independent variables. Subsequently, weighted scores were used for all questions other than global health, and stepwise regression was used to identify the questions that correlate most closely with children's disutility. The variables identified within stepwise regression as having most impact on QoL were then included within a non-stepwise regression analysis to calculate coefficients and generate predictions.

Stepwise OLS regression suggested that the seven OM8-30 items having most impact on disutility were ear problems, breathing through mouth, parents' energy, hearing in groups, global health rating of 'fair', mispronouncing words and unhappiness. The reduced model that included only the seven variables selected using stepwise regression explained 64% of variability in disutility and produced good predictions (MAE_{Val}: 0.132). Although all coefficients had logically plausible signs, this reduced model nonetheless omits a large number of questions and facets of the OM8-30 that are likely to affect children's health-related QoL, such as behaviour, concentration, sleep and progress at school.

Both an OLS model that included all nine OM8-30 facet scores plus predicted HL and an OLS model using the two domain scores plus RHD and HL as the independent variables produced reasonably accurate predictions. However, the facet score model produced more accurate predictions than the domain score model (MAE_{Val}: 0.134 for the

facet model and 0.152 for the domain model) and also fitted the data better (adjusted r^2: 0.625 for the facet model, versus 0.592 for the domain model). (Both models use suppressed constants.)

Although the item-level model had a slightly lower MAE_{Val} than the facet or domain models, item scores were not used in subsequent analyses as models using only a subset of the OM8-30 questionnaire are likely to omit some aspects of the disease that are important predictors of health-related QoL. As both the domain-level and facet-level models performed reasonably well, both were taken forward to Stage 2.

Stage 2: Investigations into the optimal functional form

A variety of functional forms were evaluated using either facet scores or domain scores of the OM8-30 as predictors of children's HUI3 disutility.

Analyses of a number of OLS models demonstrated that suppressing the constant term substantially improved model fit and slightly improved the accuracy of the predictions. For example, when data were analysed at the level of facets, suppression of the constant term increased the adjusted r^2 from 0.39 to 0.63 and reduced MAE_{Val} from 0.1364 to 0.1338. Constants were therefore suppressed in all subsequent OLS models.

Generalised linear models were investigated to assess whether they produced more accurate predictions of the positively skewed (skewness: 0.737) disutility data than OLS models that assume data to be normally distributed. GLMs with a gamma family distribution for HUI3 disutility (link identity) did not converge, regardless of whether facet or domain scores were used as explanatory variables. However, GLMs that assumed that HUI3 disutilities had a log-normal distribution converged and produced reasonable predictions. As was the case for OLS models, the GLM using OM8-30 facet scores predicted HUI3 disutilities slightly more accurately than a GLM domain score model (MAE_{Val}: 0.141 and 0.145 respectively). As well as generating less accurate predictions than the OLS facet score model, the GLMs systematically underestimated utilities for the 128 patients (36%) with perfect health (maximum predicted utility: 0.97). As they generated biased and less accurate predictions than OLS models, GLMs were considered inferior to OLS in this setting and were not investigated further.

Two-part models were also investigated as a potential solution to the skewed disutility data. In Part 1, logistic regression predicted whether children had perfect health at each time point based on either domain or facet scores. The domain score model correctly classified 80.5% of observations in the estimation data set and had an MAE_{Val} of 0.137. The facet score model correctly classified 80.3% of observations in the estimation data set and had an MAE_{Val} of 0.153; in addition to being less accurate than the domain score model, the coefficient for respiratory symptoms was also negative. The first part of the two-part model was therefore based on the model including domain scores (DEV, PHYS, RHD and HL).

In Part 2, the disutility of those patients who did not have perfect health was estimated. An OLS model based on facet scores had an MAE_{Val} of 0.142 and was therefore superior to the OLS domain score model for this part (MAE_{Val}: 0.171), although the facet model estimated the coefficient for sleep to be negative. GLMs of facet scores were also investigated: a model assuming HUI3 disutility to have a gamma distribution failed to converge, while a log-normal GLM of facet scores produced slightly inferior predictions to the OLS model for this part (MAE_{Val}: 0.162), although all coefficients were plausible.

Combining the best model for Part 1 (logistic regression using domain scores) with the OLS facet model for Part 2 produced predictions of utility that had an overall MAE_{Val} of 0.129. Although MAE_{Val} for this two-part model was slightly lower than that for the one-part facet score OLS model (0.134), this two-part model had a higher MSE_{Val} (0.02967 versus 0.02947 for the one-part OLS facet model), which indicates that large errors were more common in the two-part model than in the OLS model. This is highlighted by the fact that 16% of predictions from the two-part model deviated from observed values by more than 0.25, compared with 14% for the one-part OLS facet model. The two-part model also systematically underestimated utilities: the total error for the two-part model was –0.02 compared with –0.005 for the OLS one-part facet model. Additionally, the two-part model predicted that only 1.2% (5/406) of patient observations would have utilities between 0.90 and 0.99, whereas 17.3% (61/352) of observed utilities and 18.8% (76/404) of predictions from the OLS facet model fall in this range. Due to these distributional problems and the unreliability of the model for Part 2, the marginal increase in accuracy

achieved by the two-part model (MAE_{Val}: 0.129 versus 0.134 for the one-part facet model) was not considered to merit the additional complexity.

The model specification used in Stage 3 therefore comprised OLS models with suppressed constant using OM8-30 facet and domain scores as predictors of utility.

Stage 3: Impact of including age and sex in the model

Following the choice of functional form, an additional analysis tested the impact of controlling for age and sex on the accuracy of predicted disutilities. Although neither age nor sex was found to have a statistically significant impact on disutility, including these terms within the domain-level OLS model improved the accuracy of predictions, reducing the MAE_{Val} from 0.152 to 0.148. However, this was not the case for the facet-level OLS model, for which the MAE_{Val} rose from 0.134 to 0.140 when age and sex were included.

Stage 4: Performance of the final model

It was therefore concluded that the two models that best fitted the relationship between OM8-30 scores and HUI3 disutility were:

1. The OLS model with suppressed constant that included the DEV and PHYS domains of the OM8-30, plus the RHD facet, predicted HL, age and sex [referred to hereafter and in the main report as the (HUI3) 'domain model'].
2. The OLS model with suppressed constant that included the nine OM8-30 facets (global health, ear infections, sleep, respiratory symptoms, schooling concerns, speech/language, behaviour, parent QoL and RHD) plus predicted HL [referred to hereafter as the (HUI3) 'facet model'].

The coefficients of these models are shown in *Table 32*. The facet model fitted the data well (adjusted $r^2 = 0.626$) and was highly significant overall ($p < 0.0001$ based on F-test). However, only three facets were found to be statistically significant: ear problems ($p < 0.001$), RHD ($p < 0.001$) and parent QoL ($p = 0.030$), although all had the expected signs.

The domain model for the HUI3 disutility had an adjusted r^2 of 0.597 and a root MSE of 0.178, which are also similar to mapping models reported previously.[119] As expected, increases in the DEV and PHYS domain scores or in the RHD facet score were associated with increased disutility (lower QoL), while the objective measure (predicted HL) had a negative coefficient as this parameter adjusts for any bias (optimism/pessimism) in parents' estimates of RHD (see *Table 32*). There was a non-significant trend suggesting that older children and girls tended to have lower QoL. However, only three parameters within this model reached statistical significance: PHYS ($p = 0.001$), RHD ($p < 0.001$) and predicted HL ($p = 0.049$), although an F-test evaluating the model as a whole was highly significant ($p < 0.0001$).

The domain model including age and sex was reanalysed separately using data for each time point to assess whether coefficients were constant over time. This suggested that the impact of RHD, HL and gender was relatively consistent across the three time points, with coefficients differing from those calculated in the cluster analysis by no more than one standard error. Although administration of a potentially beneficial treatment might be expected to alter the extent to which parents over- or underestimate any hearing problem their child experienced, the consistency of RHD and HL suggests that this aspect of the placebo effect was minimal in the GNOME trial. However, the importance of the PHYS and DEV domains varied substantially over the course of the trial. At baseline and at 9 months, DEV had a statistically significant relationship with disutility ($p \leq 0.011$), while PHYS had no significant contribution. By contrast at the 3-month follow-up (immediately after the end of treatment), the relationship between PHYS and disutility reached statistical significance ($p < 0.001$), while the coefficient for the DEV domain score was small and negative ($p = 0.567$). Although these analyses provide insights into how the relative importance of the domains can vary in a clinical trial setting, the number of observations available at each time point is relatively small, and the variations observed during the GNOME trial may differ from those in other studies or routine clinical practice. The size of the data set at individual time points ($n = 61$–79 for the estimation data set) was insufficient to conduct similar analyses for the facet model.

Predicted utilities correlated reasonably well with observed values: both for the facet-level model ($r^2 = 0.43$) and the domain-level model ($r^2 = 0.39$; *Figure 32*). However, both models overestimated utility for children whose QoL was worse than average, and underestimated utility for children with perfect health; this has also been observed in previous mapping studies.[119]

TABLE 32 *Summary of the final model used to map OM8-30 scores onto HUI3, HUI2 and EQ-5D disutility values in the mapping analysis. An OLS model with suppressed constant was used on the estimation data set (75% of observations) using the cluster command*

					95% CI	
Variable	**Coefficient**	**Robust SE**	**T**	***p*** **> t**	**Lower**	**Upper**
Facet-level model of HUI3 disutility (n = 203 observations of 109 children, adjusted r^2 = 0.626, root MSE = 0.174)						
Ear problems	0.0210193	0.005657	3.72	< 0.001	0.0098061	0.0322325
Sleep patterns	0.0021797	0.008534	0.26	0.800	–0.0147368	0.0190963
School prospects	0.0053970	0.018601	0.29	0.772	–0.0314724	0.0422663
Speech and language	0.0121128	0.008931	1.36	0.178	–0.0055891	0.0298147
RHD	0.0200084	0.004967	4.03	< 0.001	0.0101630	0.0298538
Respiratory symptoms	0.0003651	0.006756	0.05	0.957	–0.0130270	0.0137572
Behaviour	0.0087217	0.006296	1.39	0.169	–0.0037570	0.0212004
Parent QoL[a]	–0.0073887	0.003354	–2.20	0.030	–0.0140375	–0.0007399
Predicted HL based on ACET (dB)	–0.0009640	0.001510	–0.64	0.525	–0.0039580	0.0020299
Global health	0.0298553	0.020007	1.49	0.139	–0.0098026	0.0695131
Domain-level model of HUI3 disutility (n = 205 observations of 109 children, adjusted r^2 = 0.597, root MSE = 0.178)						
DEV score	0.063150	0.032361	1.95	0.054	–0.0009944	0.1272944
PHYS score	0.026209	0.007488	3.50	0.001	0.0113674	0.0410515
RHD	0.023491	0.005194	4.52	< 0.001	0.0131957	0.0337861
HL predicted from tympanometry (ACET)	–0.003456	0.001732	–1.99	0.049	–0.0068898	–0.0000221
Age (months)	–0.000587	0.000486	–1.21	0.229	–0.0015502	0.0003759
Female gender	–0.013630	0.028011	–0.49	0.628	–0.0691526	0.0418928
HUI2 disutility (n = 206 observations of 110 children, adjusted r^2 = 0.613, root MSE = 0.117)						
DEV score	0.040836	0.021223	1.92	0.057	–0.0012275	0.0829003
PHYS score	0.015908	0.004969	3.20	0.002	0.0060586	0.0257565
RHD	0.018122	0.003215	5.64	< 0.001	0.0117499	0.0244945
HL predicted from tympanometry	–0.002162	0.001256	–1.72	0.088	–0.0046507	0.0003267
Age (months)	–0.000479	0.000274	–1.75	0.083	–0.0010229	0.0000645
Female gender	–0.006161	0.019731	–0.31	0.755	–0.0452674	0.0329464
EQ-5D disutility (n = 212 observations of 109 children, adjusted r^2 = 0.217, root MSE = 0.157)						
DEV score	0.047292	0.017863	2.65	0.009	0.011885	0.082699
PHYS score	0.007439	0.007361	1.01	0.314	–0.007152	0.022030
RHD	–0.003912	0.003274	–1.19	0.235	–0.010400	0.002577
HL predicted from tympanometry (ACET)	0.000133	0.002291	0.06	0.954	–0.004409	0.004674
Age (months)	–0.000456	0.000384	–1.19	0.238	–0.001218	0.000306
Female gender	0.015870	0.025028	0.63	0.527	–0.033739	0.065479

All models were estimated using OLS regression with suppressed constant on the estimation data set (75% of observations) using the cluster command. The coefficients shown in this table can be used to predict children's utility based on responses to the OM8-30: utility is equal to one minus the constant term, minus the sum of the coefficients multiplied by the corresponding OM8-30 domain/facet score. For example, using the domain model, HUI3 utility is equal to: 1 – [(0.06315 × DEV) + (0.02621 × PHYS) + (0.02349 × RHD) – (0.00346 × HL) – (0.00059 × AGE) – (0.01363 × FEMALE)], where age is in months, HL is in dB, DEV, PHYS and RHD comprise OM8-30 domain/facet scores and FEMALE is a dummy variable equal to one if the patient is female and zero if he is male. Any patient with a predicted utility greater than one should be assumed to have a utility of one. It is anticipated that observed HL may be used in these equations in place of predicted HL, although this has not been validated empirically.

a Unlike other OM8-30 facets, lower scores on the parent QoL facet represent worse symptoms.

TABLE 33 *Performance of the final model used to map OM8-30 responses onto HUI3, HUI2 and EQ-5D*

		HUI3 facet model	HUI3 domain model	HUI2 model	EQ-5D$_5$ model
Results with no adjustment for negative disutility values					
Mean (range) of predicted disutility		0.190 (–0.086 to 0.534)	0.196 (–0.093 to 0.461)	0.132 (–0.063 to 0.310)	0.075 (–0.003 to 0.148)
Total error (range)		< 0.0001 (–0.353 to 0.579)	–0.0063 (–0.342 to 0.584)	0.001 (–0.222 to 0.637)	–0.002 (–0.144 to 1.547)
MAE (range): all patients		0.129 (0.001 to 0.579)	0.137 (0.001 to 0.584)	0.090 (0.000 to 0.637)	0.093 (0.001 to 1.547)
Results after adjustment for negative disutility values					
Mean (range) of *observed* utility values: observations for whom predictions can be calculated		0.822 (0.050 to 1.000)	0.824 (0.050 to 1.000)	0.877 (0.130 to 1.000)	0.928 (–0.594 to 1.000)
Mean (range) of predicted utility values: all observations		0.805 (0.466 to 1.000)	0.802 (0.539 to 1.000)	0.867 (0.690 to 1.000)	0.925 (0.852 to 1.000)
Mean (range) of predicted utility values: observations with utility data		0.817 (0.506 to 1.000)	0.815 (0.539 to 1.000)	0.876 (0.690 to1.000)	0.925 (0.856 to 0.999)
Total error (range)		–0.005 (–0.353 to 0.579)	–0.009 (–0.342 to 0.584)	–0.001 (–0.222 to 0.637)	–0.002 (–1.444 to 1.547)
MAE (range): all child observations		0.124 (0.000 to 0.579)	0.134 (0.000 to 0.584)	0.089 (0.000 to 0.637)	0.093 (0.001 to 1.547)
MAE (range): validation data set		0.134 (0.000 to 0.433)	0.148 (0.000 to 0.584)	0.098 (0.000 to 0.637)	0.104 (0.002 to 1.547)
MAE (range): estimation data set		0.121 (0.000 to 0.579)	0.130 (0 to 0.558)	0.086 (0.000 to 0.382)	0.089 (0.001 to 1.533)
MSE (range): validation data set		0.029 (0.000 to 0.336)	0.037 (0.000 to 0.341)	0.015 (0.000 to 0.406)	0.050 (0.000 to 2.393)
% all predictions deviating from observed values by more than	0.50	1.15%	1.52%	0.38%	1.12%
	0.25	14.50%	15.91%	3.41%	1.86%
	0.10	46.18%	50.00%	35.98%	26.02%

However, both models predicted mean utility reasonably accurately: among patients for whom both predicted and observed utility data were available, the mean observed HUI3 utility was 0.82, while the facet model underestimated mean utility by 0.0053 and the domain model underestimated utility by 0.0086.

As observed previously,[119] and as would be expected from predictions of a regression model, the variance around the predicted utilities was lower than that around the original sample data (SD of observed utilities: 0.21, versus 0.12–0.16 for predicted values). Furthermore, the SD around the predicted utilities was lower for the domain model (SD: 0.123) than for the item-level and facet-level models (SD: 0.147 and 0.138 respectively).

Heteroskedasticity was also observed, with the total error around the predictions increasing with decreasing values for observed utility; the correlation between total errors and observed HUI3 utility had an $r^2 = 0.66$–0.67. Absolute errors were notably higher for patients with lower than average QoL: for the facet model, children with observed utility less than or equal to 0.8 had an overall MAE of 0.174, whereas children with perfect health had an MAE of 0.079. Previous mapping studies have also reported higher MAEs at lower utility values.[120,121]

A substantial degree of multicollinearity was associated with the domain model: for which the DEV domain score and predicted HL were found to have high uncentred variance inflation factors (VIF:

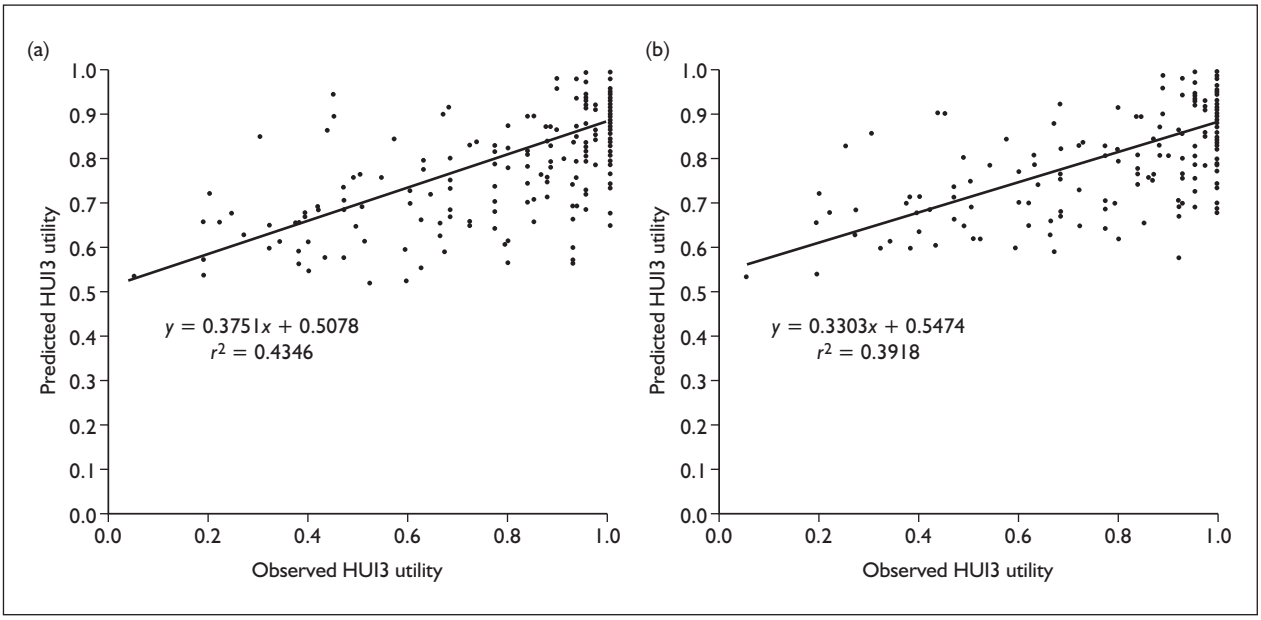


FIGURE 32 *Correlation between observed and predicted HUI3 utility. (a) HUI3 facet model. (b) HUI3 domain model plus age and sex.*

13.9 and 10.4 respectively), although the mean VIF was only 7.3. Multicollinearity was lower in the facet model, for which predicted HL was the only variable with a VIF higher than 10 and the average VIF was 4.3. However, such multicollinearity is to be expected in QoL instruments that measure different aspects of the same condition and have been designed to have internal consistency.

Although tests for omitted variables cannot be conducted in STATA following models with suppressed constant, the Ramsey RESET test was conducted after the models were repeated with the inclusion of a constant term. This test indicated that significant omitted variable bias was present in both the facet and the domain score models ($p = 0.037$ for the facet model and 0.014 for the domain score model). The omitted variables may comprise comorbid conditions that affect children's utility but are not captured on the disease-specific OM8-30 measure.

Although these diagnostic test results suggest that the magnitude and statistical significance of the coefficients should be interpreted with caution, this does not undermine the accuracy of the predictions in the validation sample, which comprises the most important criterion for model selection as these mapping models were developed solely as predictive tools, rather than to assess the relative importance of different OM8-30 facets and domains.

Stage 5: Results for other utility instruments

The two model specifications that performed best for HUI3 were used to estimate models to predict HUI2 and EQ-5D disutilities. This demonstrated that both the facet model and the domain model produced more accurate predictions for the HUI2 instrument than for HUI3 (a model of HUI2 disutilities based on DEV, PHYS, RHD, HL, age and sex), and had an MAE_{Val} of 0.098, compared with 0.148 for the HUI3 domain model (*Table 33* and *Figure 33*). However, unlike the analyses on HUI3, a model of HUI2 disutilities that included all nine OM8-30 facets plus HL did not produce reliable results, and suggested that greater problems with sleep and schooling correlated with better health-related QoL, although the facet model did have a slightly lower MAE_{Val} than the domain model (0.089 versus 0.098). Within the HUI2 domain model, 97% of predicted values were within 0.25 of the observed value, and the predicted mean utility was similar to the observed mean. However, the maximum absolute error was slightly higher for the HUI2 model than for the HUI3 domain model (0.64 versus 0.58), and the HUI2 algorithm predicted that the minimum utility value within the data set would be 0.69, compared with an actual minimum of 0.13. Furthermore, the coefficients estimated were similar across these two related utility instruments (see *Table 32*).

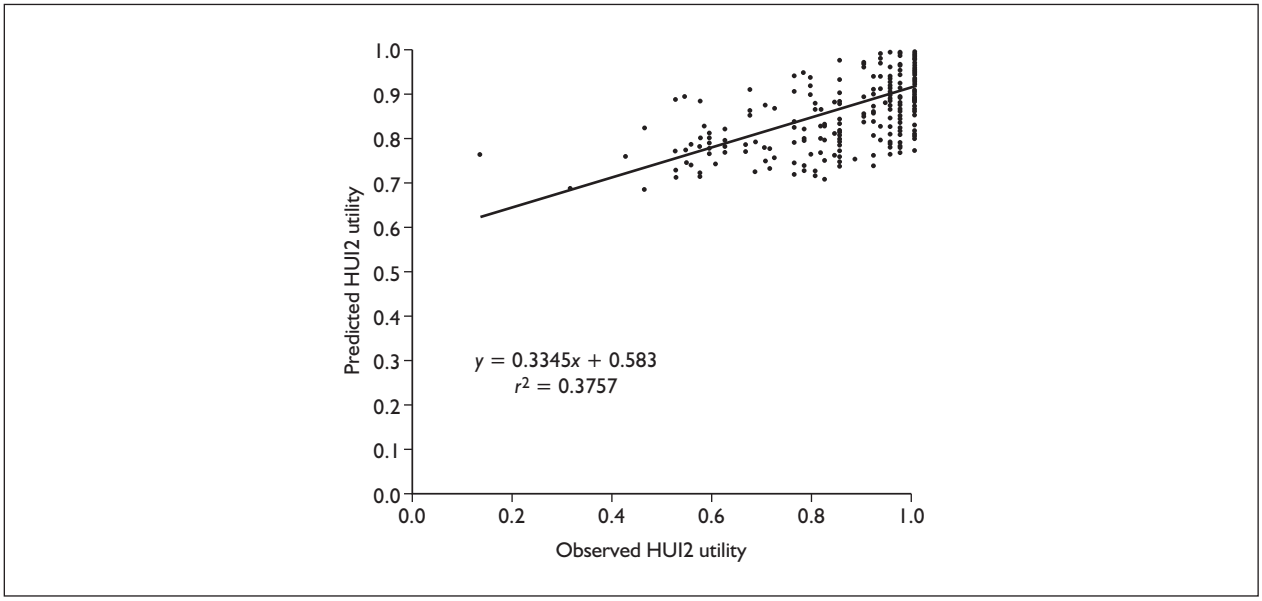


FIGURE 33 *Correlation between observed and predicted HUI2 utility.*

However, the same model specification produced a very poor fitting model of EQ-5D$_5$ disutility (*Figure 34*). For EQ-5D$_5$, the adjusted r^2 for the estimation model was just 0.22 and only one coefficient (the PHYS domain) reached statistical significance (see *Table 32*). Furthermore, although the MAE$_{Val}$ of the predicted utilities was reasonably low (0.093), it is lower than the MAE that would have been generated by simply predicting that all children had an EQ-5D utility of one (0.075). It is likely that the poor performance and low MAE of this model are largely due to the limited variability and large ceiling effect of the EQ-5D$_5$ utilities. The model fit may also have been hindered by some extreme outliers with very low EQ-5D utility that may be erroneous; in particular, two EQ-5D questionnaires indicated that the children in question had extreme problems on all five EQ-5D domains, despite achieving utilities greater than 0.9 on both HUI2 and HUI3 at the same time point and having perfect health on EQ-5D at other time points.

Limitations

- The limited sample size of the GNOME study precluded accurate estimation of item-level models and limited the accuracy with which coefficients could be estimated.
- The models have been tested against a randomly selected subset of the GNOME sample, but have not been tested on populations recruited using other methods.
- The models tended to overestimate utilities for children with poor health and underestimate those for children with very good health; although this will not affect the performance of the models within the GNOME data set, caution should be exercised when applying these models to populations with more severe disease.
- The models are based on estimated HL imputed using children's ACET measurements, rather than directly measured HL, although it is anticipated that the coefficients estimated in these models could also be used with direct measurements of HL if available.
- Although the performance of the best OM8-30 mapping models developed in this study is comparable with that of previous mapping work,[119] the predicted utilities generated using these models differ from the observed values by an average of 0.134–0.148 on the scale of HUI3 utilities, and by an average of 0.098 for HUI2 utilities. Furthermore, approximately 38.7% (37.4–40.3%) of the variability in utilities is not explained by these models of OM8-30 scores.
- Regression diagnostics suggest that the statistical significance of the coefficients may be underestimated due to multicollinearity, and that their magnitude may be influenced by omitted variables (which may include comorbidities).

Conclusions

Following evaluation of a large number of different models, a linear model predicting utility based

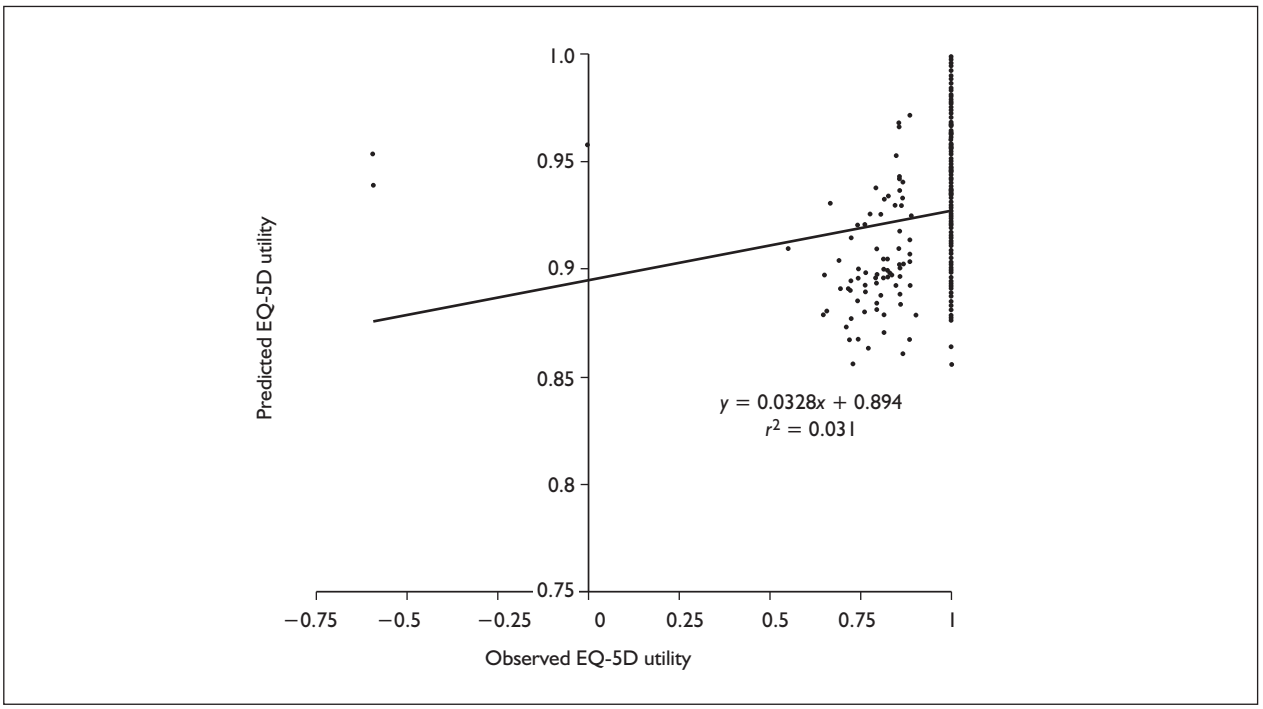


FIGURE 34 *Correlation between observed and predicted EQ-5D utility.*

on the domain scores of the OM8-30, plus HL, age and sex was identified as producing the most realistic predictions of utility. The performance of the models of HUI3 utilities was comparable with previous mapping studies[119] and produced reasonably accurate predictions of children's utility. However, HUI2 utilities correlated much more closely with OM8-30 responses than was the case for HUI3, although this may reflect the lower variability in HUI2 utilities. By contrast, no acceptable model was identified for predicting children's utility on the EQ-$5D_5$ instrument.

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.

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