# Study Protocol

## Version 1.4 (01 June 2016)

## Project title:

**Children's drops for ear pain in acute otitis media: the CEDAR Randomised Controlled Trial**

## Short title:

the children's ear pain study

## Scientific title:

**What is the clinical and cost effectiveness of benzocaine/phenazone ear drops for reducing antibiotic consumption and ear pain in children aged between 12 months and 10 years presenting to primary care with acute otitis media (AOM)? An individually randomised, placebo controlled three-arm superiority trial with cost-effectiveness analysis, qualitative evaluation and a parallel observational cohort study.**

**Trial Identifiers**

**EudraCT number:** 2014-004016-11

**ISRCTN:** ISRCTN09599764

**NHS REC reference:** 15/SC/0376

**Sponsor reference:** 2305

**Funder: NIHR Health Technology Assessment, ref:** 13/88/13

**UKCRN CPMS ID:** 30521

**CEDAR IRAS project ID:** 165404

## SIGNATURES

**WE, THE UNDERSIGNED, HAVE APPROVED THIS PROTOCOL: CHILDREN'S EAR DROPS FOR EAR PAIN IN ACUTE OTITIS MEDIA: THE CEDAR RANDOMISED CONTROLLED TRIAL AND OBSERVATIONAL COHORT STUDY**

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**Chief Investigator** **Date**

***Professor Alastair Hay, Professor of Primary Care, School of Social and Community Medicine, University of Bristol***

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**Sponsor** **Date**

***Dr Birgit Whitman, Head of Research Governance, University of Bristol***

**ACCEPTED AND APPROVED ON BEHALF OF THE UNIVERSITY OF BRISTOL**

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## 1. TRIAL SYNOPSIS

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| **Short trial title** | Children's ear drops for ear pain in acute otitis media: the CEDAR Randomised Controlled Trial and Observational Cohort Study. |
| **Scientific trial title** | What is the clinical and cost effectiveness of benzocaine/phenazone ear drops for reducing antibiotic consumption in children aged between 12 months and 10 years presenting to primary care with acute otitis media (AOM)? |
| **Phase** | IV |
| **Sponsor** | University of Bristol |
| **Chief Investigator** | Professor Alastair Hay |
| **ISRCTN** | ISRCTN09599764 |
| **EudraCT No.** | 2014-004016-11 |
| **REC Reference** | *To be provided* |
| **Medical condition under investigation** | Acute otitis media (AOM) |
| **Purpose of trial** | The main aim of the CEDAR trial is to investigate the clinical and cost effectiveness of benzocaine/ phenazone (hereon 'active') ear drops compared to 'no drops' (usual care) for reducing antibiotic consumption in children aged between 12 months and 10 years presenting to primary care with AOM.<br><br>The trial will also investigate the clinical and cost effectiveness of active ear drops compared to placebo drops for ear pain. |
| **Main research question (primary objective)** | **Primary research question:**<br>1.1 Do active drops lead to a lower proportion of children consuming antibiotics by Day 8 (where Day 1 is the day of randomisation) compared with no drops (usual care)? |
| **Other research questions (secondary objectives)** | **Key secondary research question:**<br>2.1. Do active drops provide superior pain relief in the first 24-36 hours compared to placebo drops?<br><br>**Other secondary research questions:**<br>2.2. Do active drops lead to reduced oral analgesic consumption in the first 7 days after randomisation (where Day 1 is the day of randomisation) compared with placebo drops?<br><br>2.3. Do placebo drops provide superior pain relief in the first 24-36 hours after randomisation compared to 'no drops' (usual care)?<br><br>2.4. Do active drops provide superior pain relief during Day 1 (day of consultation) compared to placebo drops? (Measured at approximately 1 hour after administration of the drops and on the evening of Day 1)<br><br>2.5. Do active drops lead to a lower proportion of children consuming antibiotics by Day 8 post randomisation compared with placebo drops?<br><br>2.6. Do active drops alter the number of days before starting antibiotics in the first seven days after randomisation, compared with placebo drops and no drops (usual care)? |

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| | 2.7. Do active drops reduce overall symptom burden (including episodes of crying/ distress, disturbed sleep, interference with normal activity, appetite and fever) in the first 7 days after randomisation compared to placebo drops and no drops (usual care)?<br><br>2.8. Do active drops alter overall illness duration (defined as the last day post randomisation on which parent-reported child ear pain scores zero for two consecutive days without other analgesic medication) compared to placebo drops and no drops (usual care)?<br><br>2.9. What are the net incremental costs to the NHS (e.g. fewer antibiotic prescriptions) and society (e.g. parental productivity) of using active ear drops compared to no drops (usual care) in the short (7 days) and medium term (3 months) post randomisation?<br><br>2.10. To conduct an economic analysis to explore whether the net incremental costs of active ear drops are justified by improved pain relief, symptom burden, antibiotic use or quality of life.<br><br>2.11. To use qualitative methods to investigate parent and clinicians' views, experiences and acceptability of the diagnosis and treatment of AOM in the CEDAR trial.<br><br>2.12. To investigate the representativeness of the CEDAR trial sample by describing the presentation, management and outcome of children with AOM in primary care. |
| **Trial design** | Individually randomised, three arm (active, placebo and no drop) superiority trial with cost effectiveness analysis and cost consequence study, and nested qualitative evaluation. Two control groups: (i) no drop (usual care, open design), because parental administration of antibiotics may be influenced by the parent's knowledge of the intervention as well as its effectiveness; and (ii) placebo, as recommended by the 2011 Cochrane Review[1] because placebo drops may have a soothing effect, and because the pain outcome is reported by parents (subjective). In addition, an observational prospective cohort study of children not included in the trial in order to assess external validity. |
| **Trial participants** | Children aged between ≥ 12 months and <10 years with ear pain due to acute (including recurrent) otitis media. |
| **Inclusion criteria** | **Trial inclusion criteria (all criteria must be met):**<br>1) Aged ≥ 12 months and <10 years<br>2) Presenting within 1 week of suspected AOM onset (other preceding respiratory tract infection symptoms may be longer)<br>3) Parent/legal guardian available to give consent<br>4) Parent-reported ear pain in 24 hours pre-enrolment (or parent-suspected ear pain if child is too young to report pain)<br>5) Clinician diagnosis of acute otitis media (although not an entry criterion, clinicians will be asked to report the presence of otoscopic evidence of acute tympanic membrane inflammation~~,~~ operationalised as per our previous trial[6] as: erythema with dullness or cloudiness; or bulging)<br>6) Child is immunocompetent |

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| | 7) Clinician willing to use a NICE-recommended 'no' oral antibiotic prescribing strategy or a 'delayed' oral antibiotic prescribing strategy (as per NICE guidelines) for the AOM and other elements of the underlying acute respiratory tract infection. NICE recommends a 'no' or 'delayed' antibiotic prescribing strategy for most immune-competent children with acute otitis media.<br>8) Parent able to give ear drops.<br>9) Parent willing in principle to use ear drops before oral antibiotics and to wait before giving delayed antibiotics as per NICE guidelines.<br>10) Parent able to report the child's ear pain.<br>11) Parent able and willing to complete daily Symptom and Recovery Questionnaire in the English language, and receive regular follow-up telephone calls, in the English language, today and every 2-3 days for up to 7 more days (or until child has been free of ear pain without medicines for two days running).<br><br>**Observational study inclusion criteria (all criteria must be met):**<br>12) Aged ≥ 12 months and <10 years<br>13) Presenting within 1 week of suspected AOM onset (other preceding respiratory tract infection symptoms may be longer)<br>14) Parent/legal guardian available to give immediate written or (if not present) telephone consent, and to provide written consent within 24 hours<br>15) Parent-reported ear pain in 24 hours pre-enrolment (or parent-suspected ear pain if child is too young to report pain)<br>16) Clinician diagnosis of acute otitis media (although not an entry criterion, clinicians will be asked to report the presence of otoscopic evidence of acute tympanic membrane inflammation, operationalised as per our previous trial[6] as: erythema with dullness or cloudiness; or bulging)<br>17) Child is immunocompetent.<br>18) Parent does not want to use trial ear drops (reason to be recorded).<br>19) Parent does not want to take part in the RCT (reason to be recorded).<br>20) Parent able to report the child's ear pain.<br>21) Parent able and willing to complete daily Symptom and Recovery Questionnaire in the English language, and receive regular follow-up telephone calls, in the English language, today and every 2-3 days for up to 7 more days (or until child has been free of ear pain without medicines for two days running) |
| **Exclusion criteria** | **Trial exclusion criteria (presence of any warrants exclusion):**<br>1) Child requires immediate hospitalisation<br>2) Child requires same day oral antibiotic treatment for AOM or other elements of the underlying acute respiratory tract infection (assess these children for observational study eligibility). NICE recommends same day antibiotic treatment for:<br>2.1) Child younger than 2 years with bilateral acute otitis media<br>2.2) Otorrhoea (discharge from the ear)<br>2.3) Child systemically very unwell or showing signs of respiratory distress (e.g. tachypnoea, hypoxia or recession)<br>2.4) Child has symptoms and signs suggestive of serious illness and/or complications (particularly mastoiditis)<br>2.5) Child is at high risk of serious complications because of pre-existing comorbidity. NICE guidelines recommend the following children are excluded:<br>2.5.1) Child has significant heart, lung, renal, liver or neuromuscular disease (defined for the purposes of this study as requiring ongoing inpatient or outpatient care from specialist teams) |

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| | 2.5.2) Child has immunosuppression (defined for the purposes of this study as a formal diagnosis of immunosuppression)<br>2.5.3) Child has cystic fibrosis<br>2.5.4) Child born prematurely (defined for the purposes of this study as born before 34 weeks and presenting within the first year of life)<br>***NB:*** *Children with other conditions who are at higher risk of AOM (e.g. Down's Syndrome, cleft palate) may take part if the Responsible Clinician feels that they meet the inclusion criteria above)*<br>3) Child requires same day oral antibiotics for another (non AOM) infection or topical antibiotic ear drops<br>4) Child is currently receiving (or has received in the past 7 days) oral or ear drop (to the AOM ear) antibiotic treatment<br>5) Suspected or confirmed tympanic membrane perforation (due to theoretical and unconfirmed risk of ototoxicity from active drops) or grommets still in situ<br>6) Known sensitivity to trial medicine (Auralgan) or to its ingredients (benzocaine, phenazone, glycerine, hydroxyquinoline sulphate) or similar substances (e.g. other ester-type anaesthetics such as procaine, tetracaine)<br>7) Known porphyria or haemoglobinopathy or glucose-6-phosphate dehydrogenase (G6PD) deficiency or methaemoglobinaemia<br>8) Known family history of G6PD deficiency (noting that G6DP deficiency is more common in African, Asian and Mediterranean populations)<br>9) Current use of sulphonamides or antimalarials or hyaluronidase or St John's Wort<br>10) Child needs to continue taking other medicinal products containing benzocaine<br>11) Child has proven alternative source(s) of pain other than and more severe than the ear symptoms with which they are presenting<br>12) Otoscopic appearances (as ascertained by clinician, where possible) consistent with observed fever, i.e. likely non-specific viral illness only (e.g. with just a slightly perfused or pink drum only)<br>13) Child has normal ear drum on examination<br>14) Child has otitis externa, or other disorder of the outer ear or tympanic membrane for which CEDAR ear drops should not be prescribed, in the AOM ear<br>15) Child has a hearing aid and parent feels hearing aid should remain in place in the AOM ear<br>16) Symptoms (i.e. hearing loss and longer duration of illness) more suggestive of a diagnosis of otitis media with effusion (glue ear)<br>17) Child has previously taken part in the CEDAR RCT<br>18) Child has taken part in any research involving medicines within the last 90 days, or any other AOM-related research within the last 30 days<br><br>**Observational study exclusion criteria (presence of any warrants exclusion):**<br>1) Child requires immediate hospitalisation<br>2) Child has proven alternative source(s) of pain, other than and more severe than the ear symptoms with which they are presenting<br>3) Otoscopic appearances (as ascertained by clinician, where possible) consistent with observed fever, i.e. likely non-specific viral illness only (e.g. with just a slightly perfused or pink drum only)<br>4) Child has normal ear drum on examination<br>5) Child has otitis externa or other disorder of the outer ear or tympanic membrane in the AOM ear<br>6) Child has a hearing aid and parent feels hearing aid should remain in place in the AOM ear<br>7) Symptoms (i.e. hearing loss and longer duration of illness) more suggestive of a diagnosis of otitis media with effusion (glue ear) |

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| | 8) Child currently taking or has previously taken part in the CEDAR RCT<br>9) Child has taken part in any AOM-related research within the last 30 days |
| **Setting:** | GP practices; Walk-in and Out of Hours Centres; and Children's Emergency Departments (which are frequently used as first point of contact for healthcare services), from hereon 'primary care'. |
| **Outcome: primary** | 1.1 Any antibiotic consumed by Day 8 (measured using daily Symptom and Recovery Questionnaire with telephone support calls during week 1), where Day 1 is the day of randomisation. |
| **Outcomes: secondary** | **Key secondary outcome:**<br>2.1. Ear pain over first 24-36 hours post randomisation using the parent completed, validated numerical rating scale successfully used in our previous trial[6] (Symptom and Recovery Questionnaire with telephone support call in first three days).<br><br>**Other secondary outcomes:**<br>2.2. Daily symptom severity (until illness resolution i.e. child free of ear pain without need for rescue analgesia for two consecutive days, expected by 8 days for most children[17]) including episodes of distress/crying, disturbed sleep, interference with normal activity, appetite, fever and hearing problems<br><br>2.3. Child completed Faces Pain Scale-Revised (FPS-R [Hicks et al 2001], for children aged ≥5 years)<br><br>2.4. Adverse events (Symptom and Recovery Questionnaire)<br><br>2.5. Time taken before oral antibiotics started<br><br>2.6. Ear drop and rescue analgesia consumption (Symptom and Recovery Questionnaire)<br><br>2.7. Parent satisfaction with, and opinion of, treatment allocation and future intention to use drops (with/without prior GP consultation if drops were to become available over-the-counter) after 7 days post randomisation<br><br>2.8. Preference based quality of child life measured (baseline, 24-36 hours, 7 days and 3 months post randomisation) using CHU-9D[18] (for children age ≥5 years)<br><br>2.9. NHS costs up to 7 days after randomisation (Symptom and Recovery Questionnaire) and contacts to 3 months (primary care medical notes review)<br><br>2.10. Child's school/nursery absences, parent lost productivity and other expenses up to 7 days after randomisation (Symptom and Recovery Questionnaire)<br><br>2.11. Child's quality of life (OMQ-14,[19] for all children aged 2 years and older) at baseline and 3 months after randomisation (postal questionnaire).<br><br>2.12. Qualitative outcomes to assess acceptability, barriers and adherence, a purposeful sample of parents and clinicians will be asked to participate in qualitative interviews to explore experiences of, and attitudes to AOM and its treatment. |

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| **Sample size** | Assuming a Type II error rate of 0.1 (90% power) and Type I error rate of 0.05 (alpha) the number of children needed in each group (active ear-drops and no- drops) ranges from 92 to 119 to demonstrate a 20% reduction in antibiotic consumption from 80-90% in the control group[8 9] to 60-70%. Using the more conservative estimate of 119, and taking into account 20% attrition, this would give a final sample size of 149 per arm. We are also interested in measuring whether the active eardrops reduce pain compared to the non-active ear-drops. Again using 90% power and alpha set at 0.05 a difference of 1.0 on the pain numerical rating scale, using an SD of 2.5 from our previous RCT[6] suggests we need 133 children in each of the active and placebo ear drop groups. Due to a delay in the manufacture of the placebo, we will start the trial as a 2 arm pilot (active drops and usual care, vs usual care/no drops), for the first 3 months of the internal pilot period, and introduce the third arm when the placebo is ready.<br><br>After assuming 20% attrition and equal numbers in the three groups we will need to recruit 167 children per arm (more than for the primary outcome) and therefore 501 children in total to the RCT. We will recruit up to an equal number of children to the Observational Cohort Study (OCS). |
| **IMP, dosage and route of administration** | Oil based benzocaine (local anaesthetic) with phenazone (analgesic) ear drops given to affected ear(s) every 1 to 2 hours until pain relieved. Both ears will be treated if AOM bilateral and rescue analgesia (oral paracetamol/ibuprofen) permitted and measured. |
| **Duration of treatment of a subject** | Treatment with trial IMP (for the two 'ear drops plus usual care' groups) until pain is relieved (NB: clinicians and parents will receive training to ensure that, should the child experience a tympanic membrane perforation after trial entry, the use of ear drops will be stopped). Based on our previous systematic review[17], we anticipate that for 50% of children the duration of treatment until pain relieved will be 3 days, and that 90% of children's symptoms will have resolved by 8 days[17]. We will ask parents to complete a daily Symptom and Recovery Questionnaire for their child's symptoms for 7 days following the day of randomisation. Parents will also receive telephone calls at four key points within the first 7 days post randomisation to support completion of the Symptom and Recovery Questionnaire: Day 1, Day 2 (24-36 hours, time point for key secondary outcome data collection), Day 6 and Day 8 (time point for primary outcome data collection). If the child's ear pain persists beyond 7 days post randomisation the parent will, if they permit, continue to be contacted by telephone twice weekly, until the child is better, in order to establish the date on which the child's ear pain had resolved for two consecutive days without medication. A review of the child's primary care medical notes will be conducted by primary care site staff at three months post randomisation. Three months post randomisation, parents will be asked to complete a postal questionnaire about the child's quality of life in the previous three months. |
| **Project timetable** | Using recent (post pneumococcal vaccine) RCGP seasonally adjusted AOM incidence data, [2] each active GP site (based on average list 6500)[3] will recruit between 0.5 and 1.3 children/month (assumes: 20% of presenting children are eligibility checked; 66% eligible; and 25% agree to be randomised). Based on experience of opportunistic recruitment in previous trials, the number of active primary care sites required to recruit 501 children is estimated to be in the range 80 -120. Due to delays in IMP procurement, recruitment will open by September 2016 and continue until the sample size has been achieved, with the first 8 trial months as an internal pilot phase, beginning with a 2 arm pilot (active drops and usual care, vs usual care/no drops) for the first 3 months, to address a delay in the manufacture of the placebo and to ensure that the trial starts by the time required by the funder. |

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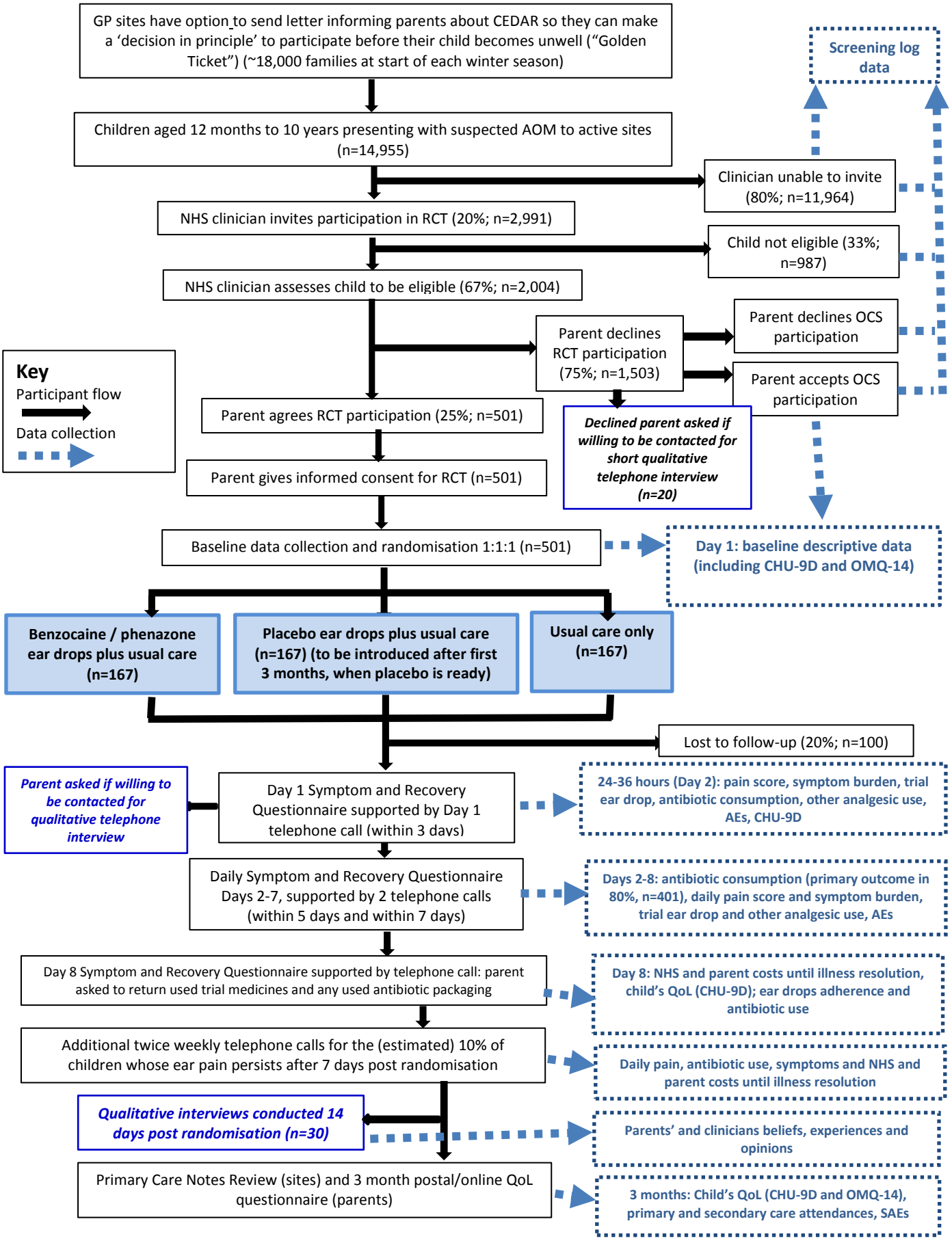
| **Team expertise** | We are four Senior Academic GPs; an Associate ENT Professor; a Reader in Statistics; a Professor of Health Economics; a Consultant in Paediatric Anaesthesia; a Consultant in Paediatric Emergency Medicine; a Qualitative Researcher and a PPI specialist, who together have considerable experience of successfully completing 'difficult-to-do' randomised trials of interventions for acute infections in children in primary care, including ENT trials. |

## 2. TRIAL PARTICIPANT FLOW DIAGRAM



## 3. LAY SUMMARY

Infection of the middle ear, termed acute otitis media (AOM), is a common, painful condition most often seen in children under 10 years. During the infection, germs multiply in the confined space of the middle ear resulting in a build-up of pressure that pushes on, and stretches the ear drum. This causes severe pain and distress to the child, leading to disrupted family life, sleep, learning and work.

Parents of children suffering with AOM frequently use painkillers (paracetamol and /or ibuprofen) and seek advice from primary care (GPs, Walk in Centres, Out of Hours Centres, and Emergency Departments). AOM is the sixth most common infectious reason for children to attend in-hours primary care, with over 500,000 consultations per annum, at an estimated NHS cost of £13.5M.

Although there is world class evidence showing that antibiotics do not help, and the National Institute for Clinical Excellence (NICE) advise against their use, over 85% of UK children with AOM are prescribed an antibiotic – a higher percentage than for any other childhood infection. This level of antibiotic use is inappropriate, unnecessary and contrary to NICE guidelines, that recommend antibiotics only for children under two who have the infection in both ears, and for children with ear discharge. The other 80% of children with AOM are unlikely to benefit from antibiotics. Furthermore, antibiotics are not pain-killers and do not treat the worst symptom of ear infections: the child's ear pain.

All of this encourages a culture of parental dependence on health care services, making them more likely to consult for future similar illness episodes, which is expensive for health care providers (consultations and prescriptions) and families (lost time from work and school, travel to primary care centres, purchase of painkilling medicines). Even more urgently, the inappropriate use of antibiotics in general practice, to which the current management of otitis media contributes, is responsible for increasing the antibiotic resistance which results in serious hospital infections such as MRSA and C. difficile, as well as undermining the potency of antibiotic medicines to treat common but potentially serious community-acquired infections. Antimicrobial resistance is now recognised by the Department of Health (DoH) and the National Institute for Health Research (NIHR) to be a very severe public health threat.

We want to find out whether pain-killing ear drops can, by treating children's ear pain, reduce the inappropriate prescribing of antibiotics for acute otitis media. The drops we wish to test contain benzocaine (numbing nerve blocker) and phenazone (pain killer). They are believed to work by directly numbing the ear drum. They can be dropped into the ear every 1 to 2 hours and are available over the counter as a pharmacy medicine in Australia, New Zealand and other parts of the world, but not in the UK.

Four previous studies have assessed the effects of single drops, but have proven inconclusive, with experts concluding that a further study is necessary. And no previous study has investigated if repeated doses (the way they are usually used in the home) reduces pain over a longer period (e.g. 24-36 hours), improves quality of life for children, reduces costs or reduces the use of antibiotics. The CEDAR trial (Children's Ear Pain Study) will address all of these issues in children attending primary care with acute middle ear infections.

## 4. INTRODUCTION

### 4.1. Background and rationale

***Concerns about primary care use of antibiotics and antimicrobial resistance***

After a fall in antibiotic use in the late 1990s, antibiotic prescribing in the UK reached a plateau and has now reversed, with rates increasing[20] and still considerably higher than those of our northern European neighbours[21] and broad agreement that prescribing rates remain inappropriately high. The relationship between primary care

prescribed antibiotics and bacterial resistance is now clear[10] with resistance lasting up to 12 months.[22] And it is not just antibiotic recipients whose bacteria develop resistance – resistant bacteria are transmitted to social contacts, which is a particular problem for young children who are unaware of hygiene conventions and who have high contact rates with other children, parents and grandparents.[23]

The inappropriate use of antibiotics and antimicrobial resistance is now at the top of England's Chief Medical Officer's and NIHR agendas. In March 2013, the Chief Medical Officer highlighted the threat posed by the rise of antimicrobial resistance to healthcare delivery in the UK.[24] In September 2013, the Department of Health published the UK's Five Year Antimicrobial Resistance Strategy and Action Plan (2013 to 2018),[25] which calls for change in the understanding and response to antimicrobial resistance by the public, the NHS, and the government in the UK. Its overarching goal is to slow the development and spread of antimicrobial resistance, by focusing on three strategic aims: (i) improving knowledge and understanding of antimicrobial resistance; (ii) conserving and stewarding the effects of existing antibiotics and (iii) stimulating the development of new antibiotics. The current NIHR themed antimicrobial resistance call for research into the evaluation of public health measures, health care interventions and health services to reduce the development and spread of antimicrobial resistance supports these strategic aims.

Conserving and stewarding the effects of antibiotics can be achieved in five ways: (i) reducing the overall quantity of antibiotics prescribed and consumed; (ii) where antibiotics are needed, promoting the use of narrow spectrum agents; (iii) where antibiotics are in demand but are ineffective, providing alternatives; (iv) reducing the transmission of antibiotic resistant bacteria and (v) vaccinating against antibiotic resistant bacteria.

***The impacts of childhood acute otitis media***

AOM is important to children, parents and the NHS for three reasons. First, the infection causes pain and distress to the child, due to a rise in pressure in the middle ear which stretches the tympanic membrane. This is important to the child and family due to disrupted sleep and time off work and school. Moreover, AOM can affect speech and hearing,[26] with effects persisting up to four times longer in those who have had AOM compared to healthy controls.[27] Although precise estimates have not previously been established for AOM, based on other acute symptom presentations,[28 29] parental costs in travel, OTC medicines and lost earnings are likely to be in the region of £15 to £30 per episode. Given that around 40%[30] of the 7.1M UK children under 10 years [6] are affected at least once per annum, this equates to an annual parental cost of at least £43M.

Second, due to the distress caused, AOM frequently results in health service consultations. Indeed, 90% of UK parents consult the NHS for each episode of AOM,[30] more than for any other common symptom of acute infection, equating to at least 2.6M consultations at a cost to the NHS of at least £50M per annum.[28 29] One UK study found that between 80% and 84% of children with AOM were prescribed an antibiotic and that this prescribing was associated with increased subsequent primary care attendance.[9] This phenomenon, known as the 'medicalisation of self-limiting illness', leaves parents more, not less, dependent on the health services due to their belief in the necessity for treatment being re-enforced by the use of antibiotics.

Finally, AOM is now the most common reason for a child to receive an antibiotic in the UK[9] and US[31] with three-quarters of UK general practices prescribing antibiotics to 80% or more of children with AOM.[8, 32] This level of antibiotic use is not surprising given the distress and associated parental pressure,[33] but is largely inappropriate, unnecessary and contrary to NICE Guidelines.[16] Evidence suggests that only younger children (<2 years) with bilateral AOM and those with otorrhoea are likely to benefit,[5] leading NICE to conclude that these are the only children warranting same day antibiotic treatment.[16] Antibiotics not only expose children to the hazards of side effects such as diarrhoea, rashes and anaphylaxis, but there is growing evidence that the risk of carrying antibiotic resistant bacteria increases substantially, and for as long as 12 months.[10] The use of a 'no' antibiotic prescribing strategy has been shown to be safe both in terms of treatment failure[34] and in the prevention of the most concerning suppurative complication of AOM, namely mastoiditis.[35]

***Concerns about the external validity of trials***

Participants in clinical trials frequently differ from the general population with the condition of interest, and it can be a challenge to determine the degree and likely effects of any selection bias. In addition to trying to minimise selection bias by encouraging practices to recruit sequential eligible children and making the trial relatively straightforward to take part in, we will seek to measure selection bias, model the effects of any selection bias, and provide data on the presentation, management and outcome of children with AOM who are not recruited into a trial, by conducting an observational study of children who are not recruited into the trial.

***Summary***

AOM is a common, painful condition of childhood. Children with AOM require adequate symptom control, including analgesia. Antibiotics are not analgesics, but are commonly used and lead to increased antimicrobial resistance and side effects. Evidence of effectiveness for alternatives to antibiotics is urgently needed to reduce reliance on antibiotics and to relieve the most common and distressing symptoms of AOM. The CEDAR trial supports the overarching goal of the UK's Five Year Antimicrobial Resistance Strategy and Action Plan (2013 to 2018), and specifically its second strategic aim, to conserve and steward the effects of existing antibiotics by investigating if an antibiotic alternative (an anaesthetic ear drop) is effective in reducing reliance on, and consumption of, antibiotics.

**4.2. Evidence explaining why this research is needed now**

***Quantitative and health economic***

Three previous trials have assessed the effectiveness of topical benzocaine/phenazone ear drops, measuring analgesic effects for up to 30 minutes after a single dose. A recent Cochrane review concluded that "the evidence from [these] RCTs is insufficient to know whether ear drops are effective".[1] Another recently published trial of shorter acting local anaesthetic (lignocaine drops) found that they were effective at 10 and 20 minutes, but not at 30.[36] We agree with the Cochrane review recommendation that benzocaine/phenazone drops should be evaluated against both placebo (to control subjective parental pain assessment) and no drops (to control for soothing effects of the oil). We are not aware of any trials assessing the effects of active drops against a 'no drop' control group. To our knowledge, none of the above trials have conducted a health economic evaluation. We searched (April 2015) the literature and trials registers and did not find any further relevant RCTs of topical benzocaine/phenazone ear drops apart from a recent US industry trial (ClinicalTrials.gov identifier: NCT02037893) investigating the effect of treatment with a combination of ear solutions (antipyrine + benzocaine otic solution, antipyrine otic solution, benzocaine otic solution and placebo solution) on the reduction of pain symptoms at 1 hour after dosing in children with acute otitis media. The results of the latter trial are not available at the time of submitting this application.

We believe the CEDAR trial is necessary and timely for three reasons. First, we hypothesise that parents will give less antibiotic medication to children whose pain and distress are adequately treated. Second, a sufficiently powered trial is needed to investigate the analgesic properties of benzocaine/phenazone drops as they would be used 'in the real world' – that is, reflecting normal repeated use in the home and thereby investigate cumulative effects over longer periods than 30 minutes. Finally, CEDAR will provide novel evidence regarding the cost effectiveness of the active drops.

***Qualitative***

Previous studies have used qualitative methods to investigate parents' views regarding AOM and antibiotics. One[37] reported that parents did not consider AOM as a significant disease threat, but did have significant informational needs. However, to our knowledge no studies have examined parents and clinician' views and experiences of AOM regarding the disease and its diagnosis and treatment in the UK context.

***Summary***

Reducing the use of antibiotics in primary care and controlling the development of antimicrobial resistance are pressing national (and international) priorities. Providing new evidence of effectiveness of symptomatic

alternatives to antibiotics, such as the anaesthetic ear drops to be investigated in CEDAR, are recognised to be key elements of improved antibiotic stewardship and could be important 'proof of principle' evidence for future trials of symptomatic treatments.

### 4.3. Justification for the trial design

***Choice of primary outcome for this study: antibiotic use***
The 'end goal' of the intervention is to reduce antibiotic consumption.

***Choice of key secondary outcome: ear pain***
Reduced antibiotic consumption is most likely to be achieved if children's pain is relieved by the ear drops, i.e. that reduction in pain is on the causal pathway to reduced antibiotic consumption. Moreover, from the parent and child's perspectives, our PPI group informs us that the effects on pain are more important than antibiotic consumption (suggesting that even if there were no effects on antibiotic consumption, the drops could still be a clinically and cost effective use of NHS resources). We will therefore measure child ear pain as a key secondary (powered) outcome.

Although we recognise that pain is an effect modifier of antibiotic use, we believe that effect modification will not be a problem in this trial as these outcomes are using different control groups for the primary outcome (the effects of active drops on antibiotic consumption will be compared against no drops or 'usual care') and for the key secondary outcome (the effect of active drops on pain will be compared against placebo drops).

***Justification for the timing (24-36 hours) of the key secondary outcome***
We want to understand the effectiveness of ear drops as close as possible to 24 hours after randomisation. Feedback from our PPI group suggested that it would be impractical for all participating parents to be able to record the child's ear pain at exactly 24 hours after entering the trial. Furthermore, we recognise the importance (for consistency and data quality) of the child's ear pain being scored by the parent rather than a child-minder or other responsible adult, and that parents will be most likely to be with their children in the evening. Following recommendations from our PPI representatives, and in order to make the collection of these data as straightforward as possible for parents, we decided to ask parents to score the child's ear pain in the evening of the day after entering the trial (i.e. on Day 2), and to record the time (24 hour clock) at which this score is made. As parents and children may be recruited on Day 1 at any time within the site's opening hours, asking the parents to provide a rating for the child's ear pain as an average over the preceding 24 hours, will give us data for the child's ear pain score at between 24 and 36 hours across the whole cohort.

***The use of a three arm trial (i.e. placebo drops arm as well as control arm)***
To fully investigate the effectiveness (including 'de-medicalising' reliance on antibiotics) an open, two arm design would be appropriate (and is part of our proposed design). However, we believe pain should also be investigated since this could explain antibiotic consumption reduction, and even in the absence of an effect on antibiotic consumption, the drops could be clinically and cost effective. Moreover, a recent Cochrane review recommended the third (placebo) arm as necessary for: (i) establishing if the active ear drop ingredients provide relief over and above the soothing effects of the oily liquid in which they are contained; and (ii) controlling for the subjective reporting of pain. This design will also allow us to establish the effects of the placebo liquid on antibiotic consumption. We have discussed the design with our PPI group and established that it is more acceptable than the two arm design since the probability of receiving drops increases from 0.5 to 0.66 and with up to two thirds of the group indicating they would want to participate.

The trial will be initiated as a 2 arm pilot (active drops and usual care, vs usual care/no drops), for the first 3 months of the internal pilot period, to address a delay in the manufacture of the placebo and to ensure the trial starts by the deadline set by the funder, with the placebo arm being introduced as soon as the placebo is ready.

***Inclusion of an observational cohort study***
The purpose of the observational study cohort is to assess external validity, since we know that screening log completion can be poor in assessing selection bias. We successfully conducted such a study in our 'GRACE' amoxicillin RCT where it did not appear to be detrimental to trial recruitment.

***Provisional recommendations dependent on trial findings***
We anticipate that:

a. If antibiotic consumption is significantly lower between the active and no drop arms, and pain significantly lower between active and placebo drop arms, we will recommend drops to both reduce pain and lower antibiotic consumption;
b. If antibiotic consumption is lower and pain the same, we will recommend active drops to lower antibiotic use;
c. If there is no difference in antibiotic consumption but the pain is significantly lower in the active than in the inactive drop arm, we will recommend active drops as a pain reduction strategy. (Even if the trial does not show a reduction in antibiotic use, if clinicians have evidence that pain is significantly less with drops, parents could be given much stronger advice about the limited utility of antibiotics - which predominantly achieve modest symptom control - and so be more confident in giving drops to lower antibiotic use in practice.)
d. If both active and placebo drops are equally efficacious, we will recommend the use of placebo drops.
e. For all other scenarios, the use of drops will not be recommended.

***Availability of trial IMP***
The CEDAR trial will use a drug which is available as a pharmacy medicine in Australia, New Zealand and other countries, but not in the UK. Therefore, if the CEDAR trial establishes evidence of clinical effectiveness, the drops will not be immediately available and may take years to become available to UK primary care. A positive result from this trial would, however, open the door to the future 'over-the-counter' availability of the drops, to be sold only after pharmacists have screened children for contra-indications to their use (principally suspected or confirmed perforation of the tympanic membrane) and instructed parents to stop using ear drops in the event of any discharge from the ear.

## 5. TRIAL OBJECTIVES AND DESIGN

### 5.1. Trial hypothesis
The use of phenazone / benzocaine ear drops (until ear symptoms are resolved with no treatment for two consecutive days) will reduce the consumption of antibiotics in children aged 12 months to 10 years with acute otitis media, compared with children receiving usual care alone.

### 5.2. Trial design
The trial will be an individually randomised, placebo controlled three-arm superiority trial with cost-effectiveness analysis, qualitative evaluation and a parallel observational cohort study, comparing phenazone / benzocaine ear drops (plus usual care) with no drops (usual care alone) in children aged 12 months to 10 years presenting with acute otitis media. The first few months of the trial will be run as a 2 arm pilot to address a delay in the manufacture of the placebo and to ensure that the trial starts by the deadline set by the funder, with the placebo arm being introduced as soon as the placebo is ready.

In this trial, parents of the children in the 'usual care' group, as well as parents of children in the two ear drops arms, will receive advice about the use of suitable analgesia and, in some instances (depending on the clinician's routine practice and judgement) a delayed antibiotic prescription and advice on its use.

***Quantitative aspects of the trial design***

CEDAR will use the randomised controlled design to minimise confounding and will be an individually randomised, three arm (active, placebo and no drop) superiority trial with a cost effectiveness analysis and cost consequence study. We propose two control groups: (i) no drops (usual care) because parental administration of antibiotics may be influenced both by knowing they are using drops, and the effectiveness of the intervention; and (ii) a placebo group as recommended by the 2011 Cochrane Review[1] as the pain outcome is reported by parents (subjective) and placebo drops may also provide pain relief.

To our knowledge, the CEDAR trial will be the first[1 36] to investigate effects of ear drops on antibiotic consumption, and will provide important, novel evidence regarding the substitution of a symptomatic treatment for antibiotics. Furthermore, previous research[1 36] has only examined the effects of single ear drop doses on ear pain over subsequent hours, but not the effects of repeated doses (i.e. normal use in the home) over longer periods (e.g. 24-36 hours).

The theoretical basis for our selection of the pain outcome is described below. We will also include parent reported episodes of distress, night disturbance and episodes of crying as these were found to be important to parents in the development phase of our previous trial of antibiotics for AOM.[6]

***Qualitative aspects of the trial design***

The combination of qualitative and controlled trial methods has long been advocated.[39] Qualitative methods are valuable to improve our understanding of the experiences of parents receiving, and staff delivering, an intervention.[40-42] Such use of qualitative methods in randomised controlled trials, specifically as part of pre-intervention development and post hoc interpretation, is well established[43-46] and recommended.[47]

In order to examine the views and experiences of AOM and its treatment, we will conduct in-depth semi-structured qualitative interviews with parents and clinicians involved in their care. Qualitative findings will help to illuminate the perceived effectiveness and acceptability of treatments and explore any barriers to their uptake outside of the trial. Qualitative methods have been chosen as the most appropriate means to achieving a deep understanding of beliefs and perceptions of key medical events.[48, 49] Interviews can explore complex and sensitive issues, allowing participants to engage in a dialogue in their own language and drawing on their life experiences to explore the issues which are important to them.

In-depth telephone interviews will be conducted with parents (from all arms of the trial) 14 days after randomisation. These interviews will consider and compare their views and experiences regarding (i) the disease; (ii) its diagnosis; (iii) treatment and recovery; and (iv) information and support needs. The qualitative study will also explore the potential implications of making the CEDAR drops available over the counter, where the costs will shift from the NHS to the individual. In addition, telephone interviews will be conducted (with consent) with those that declined trial participation or withdrew from the trial. Clinicians will be interviewed to explore their views and experiences of the trial, information and support needs and their attitudes to the future implementation of treatments.

### 5.3. Primary Research Question

The *main aim* of the CEDAR trial is to investigate the clinical and cost effectiveness of benzocaine/ phenazone (hereon 'active') ear drops compared to 'no drops' (usual care) for reducing antibiotic consumption and ear pain in children aged between 12 months and 10 years presenting to primary care with AOM.

**Main research question:**

5.3.1. **[Primary research question]** Do active drops lead to a lower proportion of children consuming antibiotics by Day 8 (where Day 1 is the day of randomisation) compared with no drops (usual care)?

**5.4. Secondary Research Questions:**

5.4.1. **[Key secondary research question]** Do active drops provide superior pain relief in the first 24-36 hours compared to placebo drops?

5.4.2. Do active drops lead to reduced oral analgesic consumption in the first 7 days after randomisation compared with placebo drops?

5.4.3. Do placebo drops provide superior pain relief in the first 24-36 hours after randomisation compared to 'no drops' (usual care)?

5.4.4. Do active drops provide superior pain relief during Day 1 (day of consultation) compared to placebo drops? (Measured at approximately 1 hour after administration of the drops and on the evening of Day 1)

5.4.5. Do active drops lead to a lower proportion of children consuming antibiotics by Day 8 compared with placebo drops?

5.4.6. Do active drops alter the number of days before starting antibiotics in the first seven days post randomisation, compared with placebo drops and no drops (usual care)?

5.4.7. Do active drops reduce overall symptom burden (including episodes of crying/ distress, disturbed sleep, interference with normal activity, appetite and fever) in the first 7 days after randomisation compared to placebo drops and no drops (usual care)?

5.4.8. Do active drops alter overall illness duration (defined as the last day post randomisation on which parent-reported child ear pain scores zero for two consecutive days without other analgesic medication) compared to placebo drops and no drops (usual care)?

5.4.9. What are the net incremental costs to the NHS (e.g. fewer antibiotic prescriptions) and society (e.g. parental productivity) of using active ear drops compared to no drops (usual care) in the short (7 days post randomisation) and medium term (3 months)?

5.4.10. To conduct an economic analysis to explore whether the net incremental costs of active ear drops are justified by improved pain relief, symptom burden, antibiotic use or quality of life.

5.4.11. To use qualitative methods to investigate parents' and clinicians' views and experiences of AOM in children in the CEDAR trial, and specifically:

5.4.11.1. To explore through qualitative methods parents' views, beliefs and expectations about AOM and its treatment.

5.4.11.2. To understand parents' and clinicians' experiences of the trial, including their experiences and opinions of treatments for AOM, including barriers, facilitators and adherence to treatments.

5.4.11.3. To examine reasons for parents' declining trial participation or withdrawing from the trial.

5.4.11.4. In preparation for disseminating the trial results, to explore the information and support needs of parents and clinicians in relation to AOM and its treatment.

5.4.12. To investigate the representativeness of the CEDAR trial sample by describing the presentation, management and outcome of children with AOM in primary care.

**5.5. Population**

Children aged 12 months to 10 years presenting to primary care with ear pain due to acute (including recurrent) otitis media.

### 5.6. Intervention and placebo

The intervention is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One mL contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). Despite an absence of published evidence of effectiveness, it is available as a pharmacy medicine in Australia and New Zealand, and has been marketed since 1947 under Auralgan© (currently manufactured by Pfizer) and other brand names. For this trial we intend to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles, or equivalent branded or bespoke manufactured product with the same constituents, against a matched placebo.

The drops are given to the affected ear or ears, according to the instructions provided with the medicine bottle, until pain is relieved - recent published evidence from our group suggests ear pain takes 3 days for 50% of children to resolve and 8 days for 90%.[17] For children with bilateral AOM, parents will be advised to treat both ears simultaneously. Parents will be given detailed instructions on how to give the ear drops, how much to administer and how often, and this will be complemented by site staff, who will be trained to support parents giving the drops. Rescue analgesia with paracetamol/ibuprofen will be permitted and measured, with parents being asked to record if being used for analgesia, fever or both.

Clinicians will receive (from the study team) clear instructions regarding the importance of not administering ear drops in the presence of any ear discharge, which may be indicative of tympanic membrane perforation (and in which case there is a theoretical but unconfirmed risk of ototoxicity), and these instructions will be passed on by clinicians to parents as part of the trial recruitment processes.

## 6. SELECTION OF TRIAL AND OBSERVATIONAL COHORT STUDY PARTICIPANTS

### 6.1. Justification for children's age range in CEDAR

Although the proposed drops are safe (no adverse events were reported in the Cochrane Review)[1] we have set the lower age limit for participation at 12 months (the final inclusion decision will be made by a GCP-trained primary care clinician). This lower age limit has been selected because of the association of fetal haemoglobin with an increased risk of benzocaine-induced methemoglobinaemia, to reduce the risk of a serious adverse event, and because establishing any diagnosis (including AOM) becomes increasingly difficult the younger the infant.

### 6.2. RCT eligibility criteria

***Trial inclusion criteria (all criteria must be met):***

1) Aged 12 months to <10 years
2) Presenting within 1 week of suspected AOM onset (other preceding respiratory tract infection symptoms may be longer)
3) Parent/legal guardian available to give consent
4) Parent-reported ear pain in 24 hours pre-enrolment (or parent-suspected pain if child too young to report pain)
5) Clinician diagnosis of acute otitis media (although not an entry criterion, clinicians will be asked to report the presence of otoscopic evidence of acute tympanic membrane inflammation, operationalised as per our previous trial[6] as: erythema with dullness or cloudiness; or bulging)
6) Child is immunocompetent.
7) Clinician willing to use a NICE-recommended 'no' oral antibiotic prescribing strategy or a 'delayed' oral antibiotic prescribing strategy (as per NICE guidelines) for the AOM and other elements of the underlying acute respiratory tract infection. NICE recommends a 'no' or 'delayed' antibiotic prescribing strategy for most immune-competent children with acute otitis media.
8) Parent able to give ear drops.

9) Parent willing in principle to use ear drops before oral antibiotics and to wait before giving delayed antibiotics as per NICE guidelines.
10) Parent able to report the child's ear pain.
11) Parent able and willing to complete daily Symptom and Recovery Questionnaire in the English language, and receive regular follow-up telephone calls, in the English language, today and every 2-3 days for up to 7 more days (or until child has been free of ear pain without medicines for two days running).

***Trial exclusion criteria (presence of any warrants exclusion):***

1) Child requires immediate hospitalisation
2) Child requires same day oral antibiotic treatment for AOM or other elements of the underlying acute respiratory tract infection (assess these children for observational study eligibility). NICE recommends same day antibiotic treatment for:
   2.1) Child younger than 2 years with bilateral acute otitis media
   2.2) Otorrhoea (discharge from the ear)
   2.3) Child systemically very unwell or showing signs of respiratory distress (e.g. tachypnoea, hypoxia or recession)
   2.4) Child has symptoms and signs suggestive of serious illness and/or complications (particularly mastoiditis)
   2.5) Child is at high risk of serious complications because of pre-existing comorbidity. NICE guidelines recommend the following children are excluded:
      2.5.1) Child has significant heart, lung, renal, liver or neuromuscular disease (defined for the purposes of this study as requiring ongoing inpatient or outpatient care from specialist teams)
      2.5.2) Child has immunosuppression (defined for the purposes of this study as a formal diagnosis of immunosuppression)
      2.5.3) Child has cystic fibrosis
      2.5.4) Child born prematurely (defined for the purposes of this study as born before 34 weeks and presenting within the first year of life)
      ***NB:*** *Children with other conditions who are at higher risk of AOM (e.g. Down's Syndrome, cleft palate) may take part if the Responsible Clinician feels that they meet the inclusion criteria above)*
3) Child requires same day oral antibiotics for another (non AOM) infection or topical antibiotic ear drops
4) Child is currently receiving (or has received in the past 7 days) oral or ear drop (to the AOM ear) antibiotic treatment
5) Suspected or confirmed tympanic membrane perforation (due to theoretical and unconfirmed risk of ototoxicity from active drops) or grommets still in situ
6) Known sensitivity to trial medicine (Auralgan) or to its ingredients (benzocaine, phenazone, glycerine, hydroxyquinoline sulphate) or similar substances (e.g. other ester-type anaesthetics such as procaine, tetracaine)
7) Known porphyria or hemoglobinopathy or glucose-6-phosphate dehydrogenase (G6PD) deficiency or methaemoglobinaemia
8) Known family history of G6PD deficiency (noting that G6DP deficiency is more common in African, Asian and Mediterranean populations)
9) Current use of sulphonamides or antimalarials or hyaluronidase or St John's Wort
10) Child needs to continue taking other medicinal products containing benzocaine
11) Child has proven alternative source(s) of pain other than and more severe than the ear symptoms with which they are presenting
12) Otoscopic appearances (as ascertained by clinician, where possible) consistent with observed fever, i.e. likely non-specific viral illness only (e.g. with just a slightly perfused or pink drum only)
13) Child has normal ear drum on examination
14) Child has otitis externa, or other disorder of the outer ear or tympanic membrane for which CEDAR ear drops should not be prescribed, in the AOM ear
15) Child has a hearing aid and parent feels hearing aid should remain in place in the AOM ear

16) Symptoms (i.e. hearing loss and longer duration of illness) more suggestive of a diagnosis of otitis media with effusion (glue ear)
17) Child has previously taken part in the CEDAR RCT
18) Child has taken part in any research involving medicines within the last 90 days, or any other AOM-related research within the last 30 days

***Inclusion of children with learning difficulties or with chronic conditions not contra-indicated by NICE guidelines***
Children with severe learning difficulties or at higher risk of AOM (e.g. children with Down's Syndrome and/or cleft palate) whose parents are able to interpret and record ear pain will be included, to maximise generalizability. We are not aware of evidence that AOM is different in these children, and the treating clinician will be responsible for deciding if children are safe to receive delayed antibiotics.

***Exclusion of children requiring same day oral antibiotic treatment***
For the RCT, only children not requiring same day oral antibiotic treatment will be eligible. In the context of this trial, a 'delayed' antibiotic will mean that both clinician and parent are comfortable in principle to try the drops first and defer antibiotics until (at least) the following day, and (at best) to only administer antibiotics if the child is not improving after three days [Little BMJ 2001]. The median duration of earache is 3 days [Thompson BMJ 2013] and our hypothesis is that drops will help parents control symptoms during this staggered decision making process. We agree that many (probably most) parents will cash the antibiotic prescription so that it is available to them, but the primary outcome is antibiotic *consumption*.

We have considered whether children requiring same day antibiotics should be eligible for the RCT, and believe they should be excluded for two reasons. Firstly, children who have been prescribed an antibiotic and told to start it immediately have very little opportunity to achieve the primary outcome (not consuming antibiotics by day 7). This risks unduly swamping the trial with children whose parents had no intention of using drops first. Secondly, children requiring same day antibiotics are likely to be more unwell – a safety issue.

Children who are already receiving antibiotic treatment at the time of presentation, or who have received antibiotic treatment within the last 7 days, will also be excluded from the trial.

***Exclusion of children requiring same day topical antibiotic treatment***
At the time of writing (January 2015) we are not aware of any UK trials of the effectiveness of topical antibiotic ear drops in primary care. However, as the indication for topical antibiotic ear drops is primarily the presence of infection that is amenable to topical treatment (i.e. (i) otitis externa, a usually painful ear condition which if present at the same time as AOM will confound the study findings, or (ii) chronic otitis media with discharge arising from a tympanic membrane perforation) children receiving topical antibiotic ear drops will be excluded.

### 6.3. Observational study eligibility criteria

***Observational study inclusion criteria (all criteria must be met):***
1) Aged ≥12 months to <10 years
2) Presenting within 1 week of suspected AOM onset (other preceding respiratory tract infection symptoms may be longer)
3) Parent/legal guardian available to give immediate written or (if not present) telephone consent, and to provide written consent within 24 hours
4) Parent-reported ear pain in 24 hours pre-enrolment (or parent-suspected pain if child too young to report pain)
5) Clinician diagnosis of acute otitis media (although not an entry criterion, clinicians will be asked to report the presence of otoscopic evidence of acute tympanic membrane inflammation, operationalised as per our previous trial[6] as: erythema with dullness or cloudiness; or bulging)
6) Child is immunocompetent.
7) Parent does not want to use trial ear drops (reason to be recorded).

8) Parent does not want to take part in the RCT (reason to be recorded).
9) Parent able to report the child's ear pain.
10) Parent able and willing to complete daily Symptom and Recovery Questionnaire in the English language, and receive regular follow-up telephone calls, in the English language, today and every 2-3 days for up to 7 more days (or until child has been free of ear pain without medicines for two days running)

***Observational study exclusion criteria (presence of any warrants exclusion):***

1) Child requires immediate hospitalisation
2) Child has proven alternative source(s) of pain, other than and more severe than the ear symptoms with which they are presenting
3) Otoscopic appearances (as ascertained by clinician, where possible) consistent with observed fever, i.e. likely non-specific viral illness only (e.g. with just a slightly perfused or pink drum only)
4) Child has normal ear drum on examination
5) Child has otitis externa or other disorder of the outer ear or tympanic membrane in the AOM ear
6) Child has a hearing aid and parent feels hearing aid should remain in place in the AOM ear
7) Symptoms (i.e. hearing loss and longer duration of illness) more suggestive of a diagnosis of otitis media with effusion (glue ear)
8) Child currently taking or has previously taken part in the CEDAR RCT
9) Child has taken part in any AOM-related research within the last 30 days

***Inclusion of children requiring same day antibiotic treatment***

We have given careful consideration to whether children requiring same day antibiotics should be eligible for the OCS, since they are not eligible for the RCT, given that the purpose of the OCS is to assess the external validity of the RCT sample.

On the one hand, we acknowledge that for some clinicians there is likely to be a difference between children whose clinicians are comfortable in using a 'no' or 'delayed' antibiotic prescribing strategy, and children whose clinicians feel that a same day antibiotic is clinically indicated. However, we also acknowledge that for other clinicians, the selection of children for different antibiotic prescribing strategies will be more arbitrary.

On balance, and in discussion with our Trial Steering Committee, we decided to include children whose clinicians opt for a same day antibiotic prescribing strategy since the OCS will then be able to:

- Gain insight into the variability of AOM antibiotic prescribing practices
- Find out what proportion of children given same day antibiotics (which will also be measured in the screening logs)
- Investigate if children receiving same day antibiotics experience a different illness trajectory and pain outcome compared to children receiving 'no' or 'delayed' antibiotics, and hence aid interpretation of the representativeness of the RCT population
- Improve OCS recruitment because fewer children would be ineligible
- Quantify the between-clinician variability in the way in which the delayed and same day antibiotic prescribing strategies are operationalised

### 6.4. Selection of participants

We recognise that to be successful CEDAR trial processes will need to be completed within routine surgery lists or within a routine care episode within the CED, WIC or OOH services. We will adopt similar methods to previous studies with similar constraints, notably the TARGET Cohort Study (http://www.targetstudy.org.uk/) led by Professor Hay, which recruited 8,400 children on time and to budget. To ensure and measure generalisability, we will use accepted techniques (e.g. asking clinicians to invite participation sequentially/at random).

***Participant invitation by GP surgeries prior to the start of the winter season(s)***

We will measure generalisability by asking all GP surgeries to record all AOM presentations and illness severity using trial specific, standardised diagnostic and illness severity codes. The numbers presented in the flow chart

(p14) were calculated to ensure we have sufficient sites given AOM incidence, which has fallen since the introduction of the pneumococcal vaccine.

Primary care AOM presentations are relatively infrequent but not rare. RCGP 2011 data suggest an average GP practice sees between 10 (winter) and 4 (summer) children with AOM per week. A key challenge will be the need for study reminders for clinicians, including: computer screen cards; electronic medical record reminder 'pop ups'; regular trial email reminders; regular trial newsletters; and identifying a 'CEDAR champion' at each practice to maintain the trial profile.

Before the start of the winter recruitment season, GP practice sites will be asked to write (via Docmail) to registered families explaining the trial and sending a Parent Information Sheet (PIS) so they can make a 'decision-in-principle' and retain a 'Golden Ticket' (a slip of printed paper, which can be affixed to the parent's fridge with a CEDAR trial fridge magnet for safe-keeping) to present to the surgery should their child become unwell with ear pain, to express their awareness of and interest in the trial. This activity will be optional for GP practices.

***Participant identification (all primary care sites)***

Primary care receptionists and triage clinicians will screen for participants when parents request appointments for children with suspected AOM, ear pain and ear rubbing (the most accurate symptoms of AOM[38]). Prompts to remind receptionists and triage clinicians will include 'ear pain CEDAR trial reminder cards' and other relevant reminders to adhere to receptionist and triage clinicians' telephones, computer screens, or desks as appropriate. Where possible, these parents will receive (by email when booking an appointment or in paper format on site arrival) a PIS to read and consider prior to receiving a full explanation from a GCP-trained primary care clinician (from here on the 'Responsible Clinician').

***Participant recruitment (all primary care sites) to the RCT***

After completing the routine consultation (from hereon the 'index consultation') the Responsible Clinician will raise the possibility of trial participation. It will be important (both for on-going trial management and assessing generalisability) to measure reasons why parents decline participation. Our qualitative study will investigate any parent concerns more fully.

For parents giving verbal consent (which will be recorded on the CRF), the Responsible Clinician will conduct and record (on the web-based data collection form) a detailed check of inclusion/exclusion criteria, brief socio-demographic and clinical details, including findings from the routine clinical examination. The Responsible Clinician may give the parent a delayed antibiotic prescription, to be used if the child's condition deteriorates or is failing to improve after an agreed period of time (our intention is for the prescription to be written, signed with the date of printing and given to the parent so that s/he can cash the prescription at their discretion, including immediately if they choose).

These details will be available to 'cut and paste' from the website to the child's electronic medical record, to minimise duplication of information recording.

***Participant recruitment (all primary care sites) to the OCS***

Parents who decline participation or whose children are ineligible for the trial will be invited to take part in an observational study. In all cases trial participation will be invited prior to extending any invitation to take part in the OCS. This is in order to prioritise entry into the RCT. Participation in the RCT would not involve any change in their management, but would involve collecting data about their presentation, management and follow-up. If parents decline participation in the observational study then they will not be entered into the study but we will record anonymous data in a screening log.

***Entry into the RCT or OCS***

Entry into the RCT or OCS will be signified by the completion of a valid consent form. Parents agreeing to take part in the RCT will be asked to sign a consent form after which the Responsible Clinician will sign the Trial Prescription

and the parent will be given the Patient Pack and, if the child is allocated to one of the two treatment arms of the RCT, the trial medicines. For parents or carers agreeing to take part in the OCS, the parent will be asked to sign a consent form, either while with the Responsible Clinician, or soon after the consultation and before leaving the site. Any patient subsequently found ineligible or declining to participate will be recorded on a screening form with brief reasons for ineligibility or declining, the remaining data destroyed and a protocol deviation recorded.

Online data collection means instant notification of recruitment to the lead Centre (Bristol). For all patients, including patients recruited using paper forms, GP sites will be asked to fax to the Bristol trial centre by the end of the same working day, evidence of valid consent and the parent's contact details. This will trigger a telephone call to the parent (usually on the same or following day) from the CEDAR trial nurse to address any questions or concerns about the trial or trial medicines.

### 6.5. Factors influencing recruitment, and how these factors will be monitored

The following six recruitment assumptions are presented for two reasons: (i) to illustrate our understanding of the challenges associated with recruiting to this trial; and (ii) to focus our recruitment strategy such that we collect detailed information to test each of the assumptions. Importantly, should recruitment be slower than expected, the collection of these data will allow us to establish which of the six recruitment steps are the problems requiring resolution, which will be achieved using our multidisciplinary team, including PPI.

a) Age and season related incidence of acute otitis media (AOM) to GP practices has been estimated from the Royal College of General Practitioners (RCGP) 2011 report for AOM in children.[2] Importantly, these estimates are post introduction, in 2006 and 2010 respectively, of the pneumococcal 6 and 13 valent vaccines (which resulted in a fall in AOM incidence) and allow adjustments for seasonal variation. We have calculated the probability of AOM presentation to general practices per quarter for a child aged 12 months to 10 years (CEDAR age criteria) to be between 0.062 (summer trough) and 0.153 (winter peak).

b) GP practice incidence has been calculated assuming an average (mean) list size of by 65003 and the proportion of children between 12 months and 10 years as 0.12 (Office of National Statistics report 0.17 of the population was aged less than 14 years in 2011).4 Therefore, we estimate an average GP practice will have between 48 (summer trough) and 119 (winter peak) children aged12 months to 10 years present with AOM per quarter.

c) Proportion of presenting children invited to participate we have assumed will be 0.2, since many children will present to primary care sites at inconvenient times (e.g. insufficient recruiting staff capacity). This proportion will be monitored by asking sites to use standard diagnostic Read codes (e.g. otalgia and acute otitis media) allowing the study team to estimate presentation rates.

d) Proportion meeting eligibility criteria we have assumed to be 0.66, since the most prevalent CEDAR exclusion criterion (bilateral AOM) was present in 34% of all children in a 2006 systematic review.[5] This is a conservative estimate since the CEDAR exclusion criterion is bilateral AOM in children under 2 years (these data not given). This proportion will be monitored through clinician completed screening logs.

e) Proportion of invited children agreeing to participate we have conservatively assumed to be 0.25, though our PPI groups suggests this may be higher, with up to 0.66 indicating they would wish to participate. This proportion will be monitored through clinician completed screening logs.

f) The proportion of children with primary outcome data we have conservatively assumed to be 0.8 (previous similar trials[6 7] have achieved proportions in excess of 0.9). This proportion will be monitored using symptom diaries.

### 6.6. Addressing recruitment challenges

We have given careful consideration to recruitment and adopted what we believe to be realistic estimates of the number/proportions of children: presenting with AOM; invited; assessed for eligibility and agreeing to participate. Recruitment will be difficult, with key challenges including: (i) relative infrequency AOM presentations; (ii) clinician equipoise and remembering to invite participation; (iii) the relatively short time available for the parent participation decision; and (iv) the short amount of time within primary care consultations to recruit.

The first and fourth challenges means that, unlike more prevalent conditions where sites can set aside staff and appointment time, CEDAR recruitment and randomisation will be conducted within consultations. We will collect only essential data, use 'easy to follow' parent instructions and same-day contact from the study team to address parents' questions. We have experience of designing such processes, as illustrated by the successful TARGET Cohort Study which recruited 8413 children from primary care.

The second challenge will be addressed through the use of clinician training in National Institute for Health and Care Excellence (NICE) guidelines and provision of systematic review evidence showing that a 'no' or 'delayed' antibiotic prescribing strategy is safe and effective for CEDAR children and the unproven value of anaesthetic drops. Clinicians will be offered paper and electronic ('pop ups' that respond to free-text (e.g. ear pain) or Read code (e.g. otalgia/otitis media) entry) CEDAR reminders. They will also be offered regular newsletters, recruitment activity tables and entry to a system of 'mini prizes' to acknowledge site recruitment contributions (e.g. site's first, fifth and tenth children; overall trial recruitment of 25$^{th}$, 50$^{th}$, 75$^{th}$ and 100$^{th}$ etc children). The web-based data collection system will facilitate real-time recruitment monitoring.

The third (and second) challenge will be mitigated by providing sites with letters and Parent Information Sheets that can be sent to registered families at the start of the winter season (if the GP practice agrees to participate in this optional activity) so that parents can make a participation 'decision-in-principle' before their child become unwell.

### 6.7. Maximising external validity

External validity is a challenge for the CEDAR trial as much as it is for other trials in general, and trials of acute otitis media (AOM) in particular. Indeed, a previous report has estimated that 44% of eligible children with AOM have been recruited to previous RCTs of antibiotics.[1]

Three of the above recruitment assumptions will be key to the trial's external validity: (i) the proportion of presenting children invited to participate (this proportion will be monitored by asking sites to use standard diagnostic Read codes (e.g. otalgia and acute otitis media) allowing the study team to estimate presentation rates); (ii) the proportion meeting eligibility criteria (this proportion will be monitored through clinician completed screening logs); and (iii) the proportion of invited children agreeing to participate (this proportion will be monitored through clinician completed screening logs). We propose to carefully record as much information about children as possible in each of these three steps in order to: (i) rectify emerging problems (to maximise external validity) and (ii) measure (so we can report) the extent of the threat to external validity.

Furthermore, we will undertake a parallel observational cohort study to the degree to which children recruited to the CEDAR RCT are representative of the population of potentially eligible children.

### 6.8. Selection of recruiting sites

Primary care: GP practices; Walk-in and Out of Hours Centres; and Children's Emergency Departments. A web-based data collection platform will mean no geographical restriction to site participation.

We will recruit children whose parents are seeking medical advice for their child's ear pain or suspected AOM in a primary care setting. Organisations will include GP practices, Walk-in and Out of Hours Centres, and Children's Emergency Departments (CEDs) where first-point-of-contact care is provided by GPs, Nurse Practitioners (NPs) and CED doctors and nurses. Through the NIHR Primary Care Clinical Research Network, we have an established

and highly functional working relationship with primary care sites across SW England and Wales. For example, the recent successfully completed HTA funded Diagnosis of Urinary Tract infection in Young children (DUTY) study co-led by Professors Hay and Butler in Cardiff worked with 273 CED and practice nurses, 182 GPs and CED doctors, and 61 research nurses at 233 primary care sites to recruit 7,374 children. This study recruited from four Centres, three of which were the same Centres contributing to the CEDAR trial.

Using recent (post pneumococcal vaccine) RCGP seasonally adjusted AOM incidence data,[2] we estimate that each active GP site (based on average list 6500)[3] will recruit between 0.5 and 1.3 children/month (assumes: 20% of presenting children have eligibility check; 66% eligible; and 25% agree to be randomised). Based on our previous experience of opportunistic recruitment to primary care trials, we estimate that the number of active primary care sites required to recruit 501 children to each of the RCT and OCS in 24 months will be in the region of 70-100.

### 6.9. Piloting recruitment

During the trial set-up stage, the trial procedures will be piloted through an iterative process where the study team will liaise closely with a number of independent primary care clinicians (to be identified through the CRN) to conduct detailed reviews of the data collection forms and procedures, and to discuss potential challenges to trial recruitment. Recruitment will be initiated in a small number of selected sites who will conduct internal piloting, i.e. establishing the efficacy of the planned recruitment procedures and materials with real patients. Due to a delay in the manufacture of the placebo, the internal pilot period will be initiated as a 2 arm pilot for the first 3 months, with the placebo arm being introduced as soon as possible. At the end of the internal pilot phase a detailed report will be sent to the funder to assess recruitment progress, assess the quality of our initial assumptions and identify any changes to recruitment strategy necessary to meet the target.

The data collected for children recruited during the internal pilot phase will be included in the trial dataset. A decision will be made as to whether to include the data for children recruited to the 2 arm pilot (for the first 3 months) will be made by the independent Trial Steering Committee based on a review of these data. Once recruitment has been proven to be effective and feasible within the initial 'piloting' sites, the placebo arm has been introduced, and any changes made in response to issues identified during this initial stage, the trial will be opened up to a wider range of participating sites.

### 6.10. Database search

During the internal pilot phase, participating GP practices will be asked to conduct a monthly database search of children presenting with AOM (using the following read codes: F527, acute right otitis media; F526, acute left otitis media; and F528, acute bilateral otitis media) in order to enable the study team to assess the proportion of presenting children who are invited to participate. (We have assumed this will be 0.2, since many children will present to primary care sites at inconvenient times, e.g. insufficient recruiting staff capacity).

### 6.11. Training and GCP requirements for recruiting sites

**Training in the trial procedures**

Each clinician who will be involved in the trial at participating primary care sites (GP practices, CEDs, WICs and OOHs) will receive training in all trial recruitment and baseline data collection procedures prior to the start of recruitment. This will include how to train parents in administering the ear drops (for parents of children allocated to one of the two treatment arms) and completing the Symptom and Recovery Questionnaire, and will be provided by trial centre teams. A clinician training log will be maintained at sites and within the Trial Master File.

Clinicians at all participating primary care sites will also be offered ongoing support, recruitment advice and refresher training on request, by the study team.

**GCP training requirements**

In order to meet the requirements of ICH-GCP, of the MHRA (see: http://forums.mhra.gov.uk/showthread.php?33-MHRA-produced-FAQs-for-Investigator-Sites) and of the Medicines for Human Use (Clinical Trials) Regulations (Statutory Instrument 2004/1031 Schedule I, part 2 [7]) that "The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor", specific arrangements will be put in place regarding the assessment of children's eligibility, the taking of informed consent and the administration of the trial IMP at recruiting sites.

These arrangements include provision for CEDAR eligibility assessments and IMP prescriptions to be made by appropriately trained (including GCP) non-medically qualified healthcare professionals, such as Advanced Nurse Practitioners/Prescribers (ANP), on the following grounds.

**Risk of trial standards falling below those of standard clinical practice:**
We have assessed the risks of ANP eligibility assessment and IMP prescription by ANPs to be consistent with the quality standards of the CEDAR trial, in line with the statements below:

1) The CEDAR eligibility criteria do not require the interpretation of diagnostic tests
2) The CEDAR recruitment processes are consistent with the responsibilities of a suitably qualified ANP within standard clinical practice
3) The diagnosis and routine management of AOM by a suitably qualified ANP is consistent with standard clinical practice
4) The prescribing of a topical analgesic by a suitably qualified ANP is consistent with standard clinical practice
5) All ANPs participating in the trial will be appropriately qualified and will be assessing and managing children with AOM as part of their routine responsibilities
6) All ANPs participating in the trial will have GCP training and will receive face-to-face training by the study team
7) All site staff roles and responsibilities will be documented on the delegation log which will be authorised by a medically qualified, GCP trained doctor.

**Availability of GCP-trained GP or other medically qualified doctor:**

8) For sites at which a GCP-trained GP or other medically qualified doctor is present, the site training and delegation logs will be authorised by this GP/doctor.
9) For Nurse-led sites at which a GCP-trained GP or other medically qualified doctor is not normally present, the site training and delegation logs will be authorised by the local CEDAR trial centre PI, acting as the GCP-trained GP.
10) Recruitment by ANPs at sites at which a GCP-trained GP or other medically qualified doctor is present will be overseen by this GCP-trained GP or other medically qualified doctor, and this oversight will take the form of GP/doctor authorisation of the completed trial prescriptions within a reasonable timescale following recruitment.
11) Recruitment from Nurse-led sites at which a GCP-trained GP or other medically qualified doctor is not normally present will be overseen by the CEDAR Chief Investigator as the medically qualified doctor. This oversight will take the form of authorisation of the completed trial prescriptions by the CEDAR CI (or another delegated GCP-trained GP, if the CI is not available) within a reasonable timescale following recruitment.
12) In all situations where a GCP-trained GP or medically qualified doctor is not available at a ANP recruitment site, if the ANP needs exceptional medical advice regarding a borderline eligility decision, the ANP will be able to contact a GCP-trained GP via the trial team through an auditable process which will be described in a SOP.

**(i) Eligibility assessment**
The eligibility of children to take part in CEDAR must be assessed by:

(a) a GCP-trained GP or other medically qualified doctor who has been trained in the trial procedures, OR;

(b) a suitably qualified and GCP-trained Nurse or other healthcare professional, who has been trained in the trial procedures, and with oversight from a GCP-trained GP or other medically qualified doctor (oversight in this instance is confirmation that the eligibility decision is correct, established by means of the GCP-trained doctor's signature on the trial prescription prior to the issue of the trial medication), OR
(c) A suitably qualified and GCP-trained Advanced Nurse Prescriber/Practitioner who has been trained in the trial procedures, with oversight from a GCP-trained GP or other medically qualified doctor (oversight in this instance is confirmation that the eligibility decision is correct, established by means of the GCP-trained doctor's signature on the trial prescription within a reasonable time scale following recruitment, as above).

**(ii) Consent**

Informed consent (which may or may not be accompanied by child assent, depending on the age and understanding of the child and at the discretion of the clinician and parent) will be obtained for all children by:

(d) a GCP-trained GP or Nurse who has been trained in the trial procedures, OR;
(e) a non GCP-trained healthcare professional (GP or Nurse) who has been trained in the trial procedures by a GCP-trained GP, and with oversight from a GCP-trained GP (oversight in this instance is: (1) written confirmation from a GCP-trained GP that the member of staff is sufficiently qualified and experienced to take consent, on behalf of the recruiting site, for this trial; and (2) countersignature on the consent form by the GCP-trained GP prior to the issue of the trial medication).

**(iii) Issue of the trial medication**

The trial medication may be issued to the parents of participating children, who have been recruited to one of the two ear drop arms, by a suitably qualified and GCP-trained GP, Nurse or other healthcare professional who has received training in the trial procedures.

Persons authorised to undertake the above activities on behalf of the recruiting site, will be documented on the trial delegation log.

Evidence of GCP training or renewal of initial GCP training, in line with local CCG practice (for Wales, we will refer to the normal practice of the Local Health Board via NISCHR), and within the last five years, will be requested and stored in the Trial Master File. The study team will provide support to recruiting sites in identifying locally available GCP training and in liaising with local CRN staff to ensure that this is made available to participating clinicians.

## 7. TRIAL MEDICINES

### 7.1. Investigational Medicinal Product and Comparator

The Investigational Medicinal Product (IMP) for this trial will be Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles, or equivalent branded or bespoke manufactured product with the same constituents, against a matched placebo. Auralgan© is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) otic solution (ear drop), sold in 15mL bottles and containing 14 mg/mL (1.4%) of benzocaine and 54mg/mL (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). The manufacturing authorisation for Auralgan is AUST R 10460 and this is held by Pfizer Consumer Healthcare (Australia). The supplier contracted for the trial (Albany Molecular Research Inc) will be responsible for the importation of the active IMP and for the manufacture of the placebo. Placebo solution will be manufactured to match the active solution for appearance, weight, texture and packaging, such that allocation concealment and blinding of the trial is maintained.

### 7.2. Packaging, labelling and dispensing

The supplier will be responsible for packaging the active and placebo medicines into identical containers and for labelling them under their MIA (IMP) license. The labelling of medication packs will be MHRA-approved and conform to Annexe 13 (GMP) and Article 13.3 of Directive 2001/20/EC. A template label will be provided by the supplier and approved by UH Bristol Pharmacy on behalf of the Sponsor in line with the Service Level Agreement (SLA), and by the Chief Investigator.

Each Medication Pack will have a Medicine ID number, randomly generated to ensure active and placebo ear drop solution bottles are indistinguishable (e.g. avoid all placebo bottles being assigned an odd number) and thus maintain allocation concealment. This random number will be generated by the Bristol Randomised Trials Collaboration and provided to the supplier who will use it to form the medicine identifier (Medicine ID Number) and include it with the open code break document sent with each delivery of trial Medicine Packs to UH Bristol Pharmacy. Each Medicine Pack will contain two bottles of either the active or the placebo solution.

The Medicine Packs will be received from the supplier and stored by the Pharmacy at University Hospitals Bristol NHS Foundation Trust (UH Bristol Pharmacy). A randomisation schedule will be provided to the supplier and to UH Bristol Pharmacy by the Bristol Randomised Trials Collaboration (BRTC) assigning active vs. placebo treatment to each Participant ID number (an interim 2-arm randomisation schedule will be applied for the 2 arm pilot at the start of the trial). The Participant ID number will have two digits will be configured to identify whether the child has been recruited into the RCT or OCS, the trial Centre in which they were recruited, followed by a sequence of digits.

All RCT Patient Packs will be pre-labelled with the Participant ID number and will contain: (i) either a medicine pack (containing either 2 bottles of active solution, or 2 bottles of placebo) or an ethically approved non-medicinal item of equivalent weight, in order to maintain clinician concealment up to the point of randomisation; (ii) relevant items of trial paperwork (including the Symptom and Recovery Questionnaire and Trial Participation Card) and equipment (including a trial pen, a small gift appropriate for participating children, and a trial tote bag), and (iii) an appropriate number of pre-printed Participant ID number labels to affix to the trial paperwork for subject identification purposes. All OCS Patient Packs, also pre-labelled with the Participant ID number, will contain items (ii) and (iii) only. The Bristol trial centre will make up the patient packs (minus the medicine packs) and provide them to UH Bristol Pharmacy. UH Bristol Pharmacy will add to the Patient Packs a Medicine Pack in line with the randomisation schedule provided by BRTC. UH Bristol Pharmacy will keep a log of which Medicine Pack is allocated to which Patient Pack and will affix the appropriate Medicine ID and Participant ID numbers to the Trial Participation Card. Complete, sealed Patient Packs will be stored by UH Bristol Pharmacy and released by a pharmacist to the Bristol trial centre in batches for direct onward distribution to recruiting primary care sites.

The Bristol trial centre will supply all participating primary care sites (including those led by Cardiff or Southampton) in small batches (of two RCT Patient Packs for the 2 arm pilot, increasing to batches of 3 once the placebo arm is introduced size to be confirmed), via same-day courier service in line with all applicable regulations. The Bristol trial centre will be the single point of contact for UH Bristol Pharmacy for the purposes of the trial. The Bristol trial centre will keep a log of which Patient Packs are sent to which recruiting primary care site, with all Patient Packs signed for on receipt at the GP practice and a faxed, completed requisition and transfer form will be sent to the Bristol trial Centre detailing the Participant ID numbers received at the site. Sites will liaise with their local Centre when more packs are required, and the local centre will then make a request for additional packs to the Bristol Centre, which will send a further batch directly to the recruiting primary care site.

From the point at which the placebo is available, participating sites will be transferred from the 2 arm pilot into the 3 arm trial once they have used up their allocation of 2 arm Patient Packs. Any new site joining the trial after the point of placebo availability will be set up to run the 3 arm trial.

Recruiting primary care sites will store the medicines in the manner approved by the MHRA and protect them from light and excessive humidity.

On completion of the baseline questionnaire (CRF) online the clinician will enter the Patient ID number.

### 7.3. Storage and transport

The product information supplied by the manufacturer (Pfizer Australia) indicates that the medicine should be stored under 25°C. We intend to store and transport the medicines in line with standard clinical shipping and storage practice in the country of manufacture and as approved by the MHRA for use in this trial. The supplier will be responsible for importing the active medicine and for ensuring that the product has not suffered any loss of quality on receipt in the UK.

The storage environment will be secure (i.e. a locked cabinet or room) with access limited to members of the practice team recorded as being involved in the trial.

A formal trial risk assessment will be undertaken for each location at which the trial medicines will be stored.

### 7.4. Dosing regimen

According to the randomisation schedule for the full trial, a child participating in the RCT will receive either active ear drops, placebo ear drops or no drops (children participating in the initial 2 arm pilot will receive either active ear drops or no ear drops). Children participating in the OCS will not receive any ear drops.

For children allocated to either of the two treatment arms within the RCT (active ear drops plus usual care, or placebo ear drops plus usual care), the allocation will be unknown to the clinician, parent, child and to the research team (with the exception of the Trial Pharmacist at UH Bristol Pharmacy). For children recruited during the 2 arm pilot, allocation to active ear drops will be known at the point of recruitment, following the assessment of eligibility and informed consent processes.

Regardless of allocation, parents in the two treatment arms will be asked to administer the ear drops no more than every 2 hours and a maximum of 12 times daily, in one or both ears to a maximum age-specific dosage per child, until pain is relieved, and for a maximum of 8 days. Missed doses should not be compensated for by giving a larger dose or more frequent doses. Clear dosage instructions will be provided on the medicine bottle and in the trial instructions for parents on how to give ear drops.

We anticipate that for 50% of children the duration of treatment until pain relieved will be 3 days, and that 90% of children's symptoms will have resolved by 8 days[17].

There are no special dietary or other requirements to be imposed.

### 7.5. Drug accountability

A formal SOP will be developed to detail the processes and documentation associated with each step.

| Activity | Responsibility |
|---|---|
| QP release of medicine packs labelled with Medicine Pack ID and Participant ID in line with randomisation schedule provided by BRTC | Supplier |
| Put together Patient Packs, minus the trial medicines but identified by unique Participant ID numbers, and supply to UH Bristol Pharmacy | Bristol Centre |
| Receive Medicine Packs (identified by unique Medicine ID numbers and Participant ID numbers, in line with BRTC randomisation schedule) from supplier | UH Bristol Pharmacy |
| Allocate Medicine Packs to Participant Packs as per randomisation schedule, and attach Medicine ID/Participant ID label to Trial Participation Card | UH Bristol Pharmacy |

| Activity | Responsibility |
|---|---|
| Send Patient Packs (numbered by Participant ID number, in batches, to Bristol trial centre via same-day courier service | UH Bristol Pharmacy |
| Receive Patient Packs from UH Bristol Pharmacy and store appropriately | Bristol Trial Centre |
| Send Patient Packs to sites via same-day or next-day (but not Friday-Monday) courier service | Bristol Trial Centre |
| Receive Patient Packs and associated medicines from Bristol trial centre and store appropriately | Sites |
| Prescribe and dispense medicines to the parent, and record the dispensing information on the GP site drug accountability log | Sites |
| Order more supplies | Sites from Bristol Centre. Bristol Centre from UH Bristol Pharmacy |
| Return of unused trial medicines | Parents will return unused medicine to Bristol centre in a stamped addressed envelope. Bristol centre will deliver to UH Bristol Pharmacy |
| Destruction of unused trial medicines | UH Bristol Pharmacy |
| Unblinding | UH Bristol Pharmacy |

### 7.6. Subject compliance

Adherence to medication will be measured using a daily Symptom and Recovery Questionnaire similar to those used in our previous trials [6,7] and primary analyses conducted on an intention to treat basis.

Subject compliance will be measured in two ways:

- The parent will be asked, at each of the 8 time points within the Symptom and Recovery Questionnaire (post recruitment on Day 1; in the evening, i.e. 24-36 hours post recruitment on Day 2; every evening for Days 3-8), how many times they have administered the trial medicines to either ear of the child. The completion of the paper or online Symptom and Recovery Questionnaire will be supported by regular telephone calls from the study team (*frequency and time points of these telephone calls to be decided in line with PPI input and subject to parental preferences*).
- Once the child's ear pain has resolved and the parent has no further use for the trial medicine, the parent will be asked to return the ear drops bottle to the study team. Prepaid, addressed packaging will be provided to parents for this purpose. Adherence will be measured by weighing the liquid remaining in the ear drop bottles.
- The parent will also be asked to record the child's antibiotic consumption at each of the 8 time points within the Symptom and Recovery Questionnaire (Days 1-8), and to return the packaging of any antibiotics used to the study team at the same time as the used ear drops. Again, parents will be provided with specific prepaid return packaging for this.

In the event that the drops are effective, it is possible they will be used more frequently in the active than control arms and adherence data will allow a secondary 'per protocol' analysis.

### 7.7. Use of alternative rescue therapies i.e. oral analgesics

Our PPI group has confirmed that parents will wish to use rescue therapy in the event of ongoing pain. Responsible Clinicians will be asked to provide standardised advice regarding the stepped use of oral analgesics, starting with: (i) paracetamol; (ii) switching to ibuprofen;[11] and (iii) using both together or alternating.[12] If the drops provide effective analgesia then it is likely that oral analgesic use will be higher in the placebo group and this could reduce the observed effect of active drops on pain. We will measure use of rescue paracetamol, ibuprofen and other pain-killing therapies (through the Symptom and Recovery Questionnaire) and both adjust for any differences between groups in our multivariable model (if necessary), and investigate the relationship between the contemporaneous use of ear drops and other analgesics (including interactions) on outcomes.

### 7.8. Concomitant medication

See exclusion criteria (which are informed by the 'interactions' stated in the Australian Government Department of Health Therapeutic Goods Administration (TGA)-approved Product Information, Appendix 8).

At the discretion of the responsible clinician, and in line with NICE guidance, parents may be offered either no antibiotic, a delayed (rescue) antibiotic prescription or a same day antibiotic prescription (of the clinician's choice). For children recruited to the RCT or OCS, parents in receipt of a delayed antibiotic prescription will be advised to delay giving antibiotics to the child as per NICE guidelines. Children will continue medication for other acute and chronic conditions as advised by their GP as long as these are consistent with the eligibility criteria. Parents will be advised not to use other benzocaine-containing products while using the trial ear drops.

### 7.9. Known side effects

According to the SmPC equivalent provided by the manufacturer (received direct from Pfizer, Australia on 09 December 2015), which is the TGA-approved Product Information for Auralgan Ear Drops (PI-Auralgan_2015-05-07A, approved by TGA on 16 April 2014, and last updated on 03 July 2015; see Appendix 8), no known, expected side effects are associated with the use of Auralgan.

Furthermore, the known side effects associated with topical benzocaine or phenazone application reported in the Product Information are rare and considered to be "unlikely following application of Auralgan on the external ear canal".

A detailed review of the safety risks of Auralgan, specifically focusing on the risks of benzocaine-induced methaemoglobinaemia, has been conducted by the investigators (December 2015), including a review of benzocaine-associated reported adverse reactions in the United States, Australia and the UK, and no reported serious adverse reactions were identified in which Auralgan was the primary suspected causal agent. This review included a query of the Database of Adverse Events Notifications for Australia (where Auralgan has been used as an OTC medicine for at least 50 years) which includes adverse event reports between 01 January 1971 and 19 August 2015, and this found a total of 11 reports for Auralgan during the reporting period. Although neither the age of the patients or the severity of the adverse events were reported, none of the events described in these reports corresponded to our definition of a Serious Adverse Event.

All of the information provided within the 'contraindications', 'precautions', 'interaction with other medicines' and 'adverse reactions' sections of the Product Information, as well as any information identified within the review of Auralgan/benzocaine-induced methemoglobinemia as pertaining to the theoretical risks of topical benzocaine and phenazone use, has been incorporated into the trial eligibility, training and operationalisation.

For the above reasons no adverse reactions related to the IMP are expected in this trial.

All adverse events, including any new or worsening symptoms, will be monitored in line with the trial monitoring SOP, but will only be reported if meeting the definition of a Serious Adverse Event and as per the trial Research Safety Reporting SOP (see section 8, Pharmacovigilance, below). Any SAE deemed related to the IMP will be reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR) per the trial Research Safety Reporting SOP, Directive 2001/20/EC and CT-3.

Based on previous clinical experience with Auralgan no adverse events are expected in this trial, however the trial investigators wish recruiting primary care clinicians to be aware of the theoretical safety risks associated with the use of topical benzocaine and phenazone, as stated within the 'Adverse reactions' section of the Product Information, as follows:

**<u>Symptoms / signs</u>**

- Difficulty breathing
- Pale, gray or blue coloured (bluish) skin

- Severe tiredness/weakness/fatigue/inability to do physical activity
- Confusion, light-headedness, severe dizziness or headache
- Nausea, vomiting
- Dark urine
- Yellowing of the skin and the whites of the eyes (jaundice)
- Heart murmur or increased heart rate
- Enlarged spleen; enlarged liver
- Rash; urticaria; Burning/stinging/redness/new pain in or around the ears; itching/swelling (especially swelling of the ear/eye/ face/neck/throat/mouth/tongue)
- Oedema; anaphylaxis
- Vertigo; nystagmus
- Sensitisation / irritation: erythema and pruritus which may progress to vesiculation and oozing

**Diagnoses**

- Dyspnoea
- Cyanosis
- Methaemoglobinaemia
- Phenazone-induced haemolytic anemia and agranulocytosis
- Benzocaine toxicity
- Penetration of the local anaesthetic into the inner ear
- Benzocaine hypersensitivity reaction
- Contact dermatitis due to frequent exposure to ester-type local anaesthetics
- Angioedema

A summary of the rare complications, and recommendations for the diagnosis and treatment of benzocaine-induced methaemoglobinaemia, will be provided to clinicians within the Trial Participation Card.

We will advise the parents/carers of participating children which adverse signs to watch for in the Parent Information Sheet (PIS), through the recruitment process (information to be provided by recruiting primary care staff to parents), in printed ear drops instructions that will be provided to parents of all participating children in the ear drops arms of the trial, and in the Trial Participation Card, which will also be given to the parents of all children receiving ear drops within the trial. With reference to a single adverse event reported in the DAEN (ref: 207569, reported on 03/05/2005), we will also advise parents to stop giving ear drops if they appear to be associated with an increase in pain.

Parents/carers will be made aware of the following:

- Auralgan may cause harm if swallowed.
- When used in small doses, no COMMON side effects have been reported with Auralgan.
- Patients are advised to tell their doctor in the event of:
    - any of these unlikely but serious side effects: burning/stinging/redness/new pain in or around the ears.
    - any of these rare but very serious side effects: bluish skin, severe tiredness/weakness.
    - any of the following symptoms of a rare but serious allergic reaction: rash, itching/swelling (especially swelling of the ear/eye/ face/neck/throat/mouth/tongue, a condition known as angioedema), severe dizziness, trouble breathing.

### 7.10. Return and destruction of medication

After illness resolution (i.e. when the child's ear pain has resolved for two consecutive days without rescue analgesic medication) parents will be asked to return any used and unused ear drop bottles, with any unused contents, to the trial centre. Parents will be provided at recruitment (in the patient pack) with prepaid, return addressed secure packaging with which to do this. Once returned to the trial centre, the ear drop bottles will be

weighed and the weights recorded on the Master Drug Accountability Log. Any trial medicine that is returned will be passed from the trial centres to UH Bristol Pharmacy for destruction, in line with the current UH Bristol Pharmacy Medication Disposal SOP.

Parents will also be asked to return the containers of any used antibiotic medication that has been prescribed for the child's ear pain, to the trial centre. Parents will be provided with a further prepaid, return addressed packet (in the Patient Pack) for this purpose. When received at the trial centre, the contents of any antibiotic packaging will be checked and recorded on a trial-specific antibiotic packaging log. Any unused antibiotics will be passed to the UH Bristol Pharmacy for destruction in line with the current UH Bristol Pharmacy Medication Disposal SOP.

## 8. PHARMACOVIGILANCE

Safety events will be reported in line with The Medicines for Human Use (Clinical Trials) Regulations 2004.

### 8.1. Definitions

***Adverse Event (AE)***

AEs are defined as any untoward medical occurrence in a clinical trial participant. An AE does not necessarily have to have a causal relationship with the trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (International Conference on Harmonisation [ICH] definition). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

All AEs will be recorded in the Case Report Form (CRF) for the duration of the child's direct involvement in the trial. This is 8 days, i.e. the day of randomisation (Day 1) plus the 7 succeeding days. For the 10% of children whose ear pain may be unresolved by day 7, AEs will be recorded until illness resolution, which is defined as the point at which the parent-reported ear pain score for the child has been zero for two consecutive days without medication.

***Serious Adverse Event (SAE)***

A SAE is defined by ICH as any untoward medical occurrence that at any dose of the trial medication meets any of the following conditions:

1. **Results in the death of the participant**
2. **Is life-threatening**
   The term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
3. **Requires in-patient hospitalisation or prolongation of existing hospitalisation**
   For any event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of these outcomes, the CI should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to UH Bristol (who acts on behalf of the Sponsor in these instances).
4. **Results in persistent or significant disability / incapacity**
   Any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.
5. **Is a congenital anomaly / birth defect**
   Exposure to the trial drug before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.
6. **Other medical events**

Medical events that may jeopardise the subject or may require an intervention to prevent a characteristic or consequence of a SAE. Such events are referred to as 'important medical events' and are also considered as 'serious' in accordance with the definition of a SAE.

***Adverse Event Associated With the Use of the Drug***

The relationship between the drug and the occurrence of each adverse event will be assessed and categorised as below. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. will be considered. The investigator will also consult the relevant drug safety documentation (SmPC equivalent and/or IB).

- *Not related:* Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
- *Unlikely:* Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- **Possibly related:* Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
- **Probably related:* Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
- **Definitely related:* Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

*Where an event is assessed as ***possibly related***, ***probably related***, or ***definitely related*** the event is an *adverse reaction*.

### 8.2. Procedure for reporting

All adverse event reporting will be in accordance with the UH Bristol 'Research Safety Reporting Policy' (http://www.uhbristol.nhs.uk/media/2518477/research_safety_reporting_sop_009_uhbristol_r_i_v8.0_19.10.15.pdf. A formal SOP and flowchart will be developed to describe the reporting procedure in detail.

***All Adverse Events***

All AEs will be reported by the Chief Investigator from the time a signed and dated informed consent form is obtained until completion of the patient follow-up at 28 days after randomisation. Adverse events described in the Patient Information Sheet, Protocol or in the pharmacological documentation associated with the trial drug will be monitored and recorded as non-reportable. This includes the potential incidence of tympanic membrane perforation, which may occur in up to 7% of children with AOM. The trial training and recruitment processes will be carefully designed to ensure that clinicians and parents will be vigilant to this potential problem, and parents will receive training to immediately recognise the signs that tympanic membrane perforation may have occurred (discharge from the ear, and/or sudden relief of the child's ear pain), and know what to do (stop treatment with ear drops).

If a Responsible Clinician or other member of the research team becomes aware that a trial-related SAE has occurred beyond the 28 day period this will also be reported to the Sponsor. Those occurrences meeting the definition of SAEs must be reported using the Serious Adverse Event Form, including any related SAE which a Responsible Clinician believes has occurred beyond the trial follow-up period). UH Bristol, on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by a CI.

All AEs, regardless of seriousness, severity, or presumed relationship to trial drug, must be recorded in the source document and the CRF, together with any measures taken. All Centre PIs must record in the CRF their opinion concerning the relationship of the adverse event to trial therapy. UH Bristol, on behalf of the Sponsor, assumes responsibility for overseeing the appropriate reporting of serious adverse events to the regulatory authorities, in line with the SLA.

All emerging pharmacovigilance data which may be related to activities carried out by the IMP and placebo supplier will be notified to the supplier.

***Serious Adverse Events (SAEs)***
All SAEs must be reported to the UH Bristol contact (fax 0117 3420239 or research@uhbristol.nhs.uk) and Centre PI by a delegated member of the research team within 24 hours of their knowledge of the event. The Chief Investigator and Sponsor should also be informed.

All SAEs that have not resolved by the end of the trial (i.e. by the end of the 28 days of the post-randomisation follow-up period), or that have been not resolved upon discontinuation of the participant's participation in the trial, must be followed until any of the following occurs:

- the event resolves
- the event stabilises
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the trial drug or to factors unrelated to trial conduct
- when it becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The death of a participant is considered an SAE, as is any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a participant's participation. Exceptions to this are hospitalisations for:

- social reasons in absence of an adverse event
- in-clinic protocol measures
- surgery or procedure planned before entry into the trial (must be documented in the CRF)

***Suspected Unexpected Serious Adverse Reaction (SUSAR)***
All relevant information about a SUSAR which occurs during the course of the trial and is fatal or life-threatening will be reported within 7 days to the MHRA by UH Bristol, on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics, the British National Formulary and study protocol. UH Bristol will work with the research team to support the reporting process for the NHS REC.

All relevant information about a non-fatal or life-threatening SUSAR which occurs during the course of the study will be reported within 15 days to the MHRA and the relevant ethics committee by UH Bristol, on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics, the British National Formulary and study protocol.

### 8.3. 'Expected' Adverse Events and Reactions
Any symptom, side effect or adverse event listed in the Summary of Product Characteristics will not be regarded as unexpected. However, since no known common side effects are listed in the Auralgan SmPC equivalent any adverse event deemed related to the IMP will be regarded as unexpected.

### 8.4. Treatment Stopping Rules
The trial may be prematurely discontinued by the Sponsor, Chief Investigator, Regulatory Authority or Funder on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Trial Steering Committee, who will advise on whether to continue or discontinue the trial and make a recommendation to the Sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

## 9. TRIAL PROCEDURES

### 9.1. Eligibility assessment

The eligibility of children to take part in CEDAR must be assessed by (a) a GCP-trained GP or other medically qualified doctor who has been trained in the trial procedures, OR (b) suitably qualified and GCP-trained Nurse or other healthcare professional, who has been trained in the trial procedures, and with oversight from a GCP-trained GP or other medically qualified doctor (or by an ANP with responsibility for the child's clinical care and under the conditions described in Section 6.11 above, 'Training and GCP requirements for recruiting sites').

Children's clinical data will be collected at baseline in line with the trial recruitment Standard Operating Procedure.

Prior to establishing whether the child is eligible to take part in CEDAR, verbal consent will be sought from the parent to conduct a detailed check of the eligibility criteria and this will be recorded on the CRF prior to recording whether the child meets the inclusion and exclusion criteria.

Informed consent should be obtained, and assent sought where appropriate, once the Recruiting Clinician has established that the child is eligible to take part.

### 9.2. Consent

The conduct of the trial will be in accordance with the Principles of Good Clinical Practice and applicable regulatory requirements. As all CEDAR subjects will be under 16 years of age, the legal parent or guardian's written informed consent is required for their child to participate in the trial. Sites will use the current, ethically approved version of the consent/assent forms, parent information sheet and other trial documentation.

Consent will be obtained for all children by (a) a GCP-trained GP or Nurse who has been trained in the trial procedures, OR (b) a suitably qualified other healthcare professional (GP or Nurse) who has been trained in the trial procedures by a GCP-trained GP, and with oversight from a GCP-trained GP (oversight in this instance is: (1) written confirmation from a GCP-trained GP that the member of staff is sufficiently qualified and experienced to take consent, on behalf of the recruiting site, for this trial; and (2) countersignature on the consent form by the GCP-trained GP prior to the issue of the trial medication).

***Informed consent***

Children under 16 cannot consent solely on their own behalf for an IMP study.

As routinely happens in similar paediatric clinical intervention trials, consent will be taken by a medical or a nursing registered practitioner, who will:

(i) Be competent to gain consent from parents on behalf of their children and to gain assent as appropriate from children who are competent to understand what is being asked within the study, and;

(ii) Have undertaken GCP training within 5 years (or as required by the CCG or Local Health Board), and received study-specific training prior to the start of recruitment.

It is the responsibility of the Recruiting Clinician (or other healthcare professional if local practice allows and this responsibility has been delegated by the site PI as captured on the Site Signature and Delegation Log) to obtain written informed consent for each child prior to performing any trial related procedure.

Because CEDAR requires children to be recruited opportunistically, parents may not have time to read the complete Parent Information Sheet (PIS) within the recruitment consultation. Clinicians taking consent must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the parent, and be satisfied that the parent has a full and sufficient understanding of what is

involved before being asked to give consent. The consenting clinician should also stress that the parent or child is completely free to refuse to take part or withdraw from the trial or from any specific aspect of the trial (if not full withdrawal) at any time. The parent (and child if this is appropriate) must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the parent or child to refuse to participate in the trial without giving a reason must be respected. If the child appears distressed about taking part to a degree that the clinician finds concerning, parental informed consent must be considered invalid.

If the parent is interested in taking part but requires more time to read the PIS and consider participation, the clinician may ask them to sit in the waiting room while they see the next patient, and then call the parent and child back in. The PIS will contain the names and contact details for the study team so that the parent may contact them with any queries about the research, at any time.

If the parent expresses an interest in their child participating in the trial they should be asked to sign and date the current ethically approved version of the Informed Consent Form. Children who are able to understand what is asked of them within the study may be given a copy of the Child Information Sheet and sign an assent form if age appropriate.

The consenting clinician must then sign and date the form. A copy of the Informed Consent/Assent Form should be given to the parent/child, a copy should be scanned into the child's primary care medical notes, a copy filed and the original sent to the trial centre for filing in the Investigator Site File (ISF). Once the child is entered into the trial the subject's trial number should be entered on the Informed Consent/Assent Form maintained in the ISF.

Details of the informed consent discussions should be recorded in the subject's medical notes. This should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and a copy of the Consent Form (which will include the version number of the Parent Information Sheet). Throughout the trial the parent should have the opportunity to ask questions about the trial and any new information that may be relevant to the subject's continued participation should be shared with them in a timely manner.

Details of all parents approached about the trial on behalf of their children should be recorded on the Subject Screening/Enrolment Log. For children recruited at CED, OOH and WIC sites, with the parent's prior consent their General Practitioner (GP) should be informed that they are taking part in the trial. A GP Letter is provided for this purpose.

***Assent***

In CEDAR, children of school age (≥ 5 years) are expected to complete daily pain scores within the Symptom and Recovery Questionnaire (using the FPS-R) and all children recruited into the trial and who are allocated to one of the treatment arms will receive the ear drops. Where appropriate, the child's assent (indicating understanding of what they are participating in and their voluntary participation) should be sought, supported by the separate study Assent Form and Child Information Sheet (designed for children aged 6-10 years).

At the discretion of the clinician and parent, assent should be sought as appropriate given the child's competence, for children who are able to understand what is asked of them within the study (usually around 5 to 6 years of age but may be younger or older depending on cognitive development). Assent must be obtained before randomisation and after an age-appropriate explanation has been given of the treatment options and the manner of treatment allocation.

Proceeding without assent risks contravening the legal requirement for this to not be against the best interests of the child (in other words, the child's dissent would negate the adult consent in a trial such as this where involvement should be truly voluntary at the point of inclusion). Article 28 of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/17c.pdf) states that:

*When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.*

Assent processes and expectations regarding the child's potential understanding of the risks and benefits of taking part, must also be proportionate given the requirement to recruit opportunistically within a routine consultation, and will be at the discretion of the Responsible Clinician and of the parent.

### 9.3. Patient registration information

The Recruiting Clinician will note (during the consenting process) and record on the participant registration section of the CRF (paper version only) the following information:

- The name of the child and of the consenting parent
- The name of the child's GP practice (if recruited at a CED, WIC or OOH clinic)
- The child's date of birth and gender
- The child's postcode
- The parent's first and second preference telephone numbers on which they would prefer the study team to make the telephone calls to support Symptom and Recovery Questionnaire completion, and preferred time for contact to be made.

This information will not be entered onto the clinical database but will be faxed to the secure fax machine at the Bristol trial centre. The child and parent's identifiable information will be stored by the trial team on a restricted access administrative database hosted on a secure server at the University of Bristol.

### 9.4. Baseline CRF completion

Baseline CRF data items to be collected will include medical history, symptoms, signs (to be assessed by the Recruiting Clinician), the clinician's working diagnosis and planned management, and the child's quality of life. Quality of Life will be measured for children aged ≥ 5 years using the CHU-9D. This will be done prior to randomisation in order to avoid bias.

### 9.5. Delayed antibiotic prescribing in CEDAR

***GP practices***

We will ask clinicians who intend to follow a delayed antibiotic prescribing strategy to write the prescription on the standard FP10 form, sign it as normal with the date of printing, and give it to the parent with a recommendation to wait, as per NICE guidelines, before cashing it at their local pharmacy. The parent will then be able to cash the prescription at her/his discretion (including immediately if they choose).

***Children's Emergency Departments***

In the Bristol CED, delayed antibiotic prescribing is not part of normal practice. If required for a child attending within normal working hours, an antibiotic prescription would be written and given to the parent to be cashed straight away at the hospital pharmacy. For a child attending out of hours, a prescription would be written and the antibiotics handed immediately to the parent from drug stores within the CED. For CEDAR we want to recruit those children presenting to the CED whom the clinician feels can be managed appropriately with either delayed or no antibiotic prescribing. Because standard CED prescriptions cannot be cashed in at other pharmacies, and because it would be undesirable (from the point of view of antibiotic stewardship) to give the parent an antibiotic medicine with advice to delay using it as per NICE guidelines (as opposed to delayed antibiotic prescribing in GP practices, where a prescription is given but not the antibiotic medicine), for this trial the CED will implement an alternative antibiotic prescribing process using the standard FP10 form for outpatients which can be cashed in at any pharmacy. Parents of children recruited at the CED for whom the clinician feels a delayed antibiotic is appropriate will therefore be given a standard prescription, signed for the date of printing, with a recommendation to wait until at least the following day before cashing it at their local pharmacy.

The above approach allows flexibility and promotes consistency in the operationalisation of delayed antibiotic prescribing across recruiting sites.

***Walk-In Centres and Out of Hours clinics***
The South Bristol Urgent Care Centre (UCC) is a Nurse-led out of hours / walk-in primary care provider in which same-day and delayed antibiotic prescribing is part of normal practice.

### 9.6. Randomisation and administration of patient packs

The trial medication may be issued to the parents of participating children, who have been recruited to one of the two ear drop arms, by a suitably qualified and GCP-trained GP, Nurse or other healthcare professional who has received training in the trial procedures.

Trial medicines will be administered in a manner designed to prevent loss of concealment pre-randomisation (see sections 7.2 and 12.3). Once the child has been confirmed to be eligible for the trial, and once written, informed consent has been obtained from the parent, the clinician will select the next sequentially numbered Patient Pack and open this in the presence of the parent. The presence of a Medicine Pack within the Patient Pack, vs the presence of a non-medicinal item (of equivalent weight) will indicate to the clinician whether the child has been allocated to one of the treatment (active ear drops or placebo ear drops) arms, or to the control (no ear drops) arm.

The transition from the initial 2 arm pilot, to the 3 arm full trial once the placebo is available, will be managed in order to reduce wastage of Patient Packs. From the point at which the placebo is available, participating sites will be transferred from the 2 arm pilot into the 3 arm trial once they have used up their allocation of 2 arm Patient Packs. Any new site joining the trial after the point of placebo availability will be set up to run the 3 arm trial.

### 9.7. Trial Participation Card

Each parent of children recruited to one of the ear drop arms will be provided with a Trial Participation Card detailing emergency contact numbers, to include how concerned clinicians may contact the (24/7) on-call pharmacist at the University Hospitals Bristol NHS Foundation Trust (UH Bristol Pharmacy) if requiring emergency unblinding. Parents will be requested to carry this card with them at all times whilst their child is participating in the trial and to present it to their child's Responsible Clinician in the event of an emergency.

### 9.8. Advice to parents on delayed antibiotic use

Clinicians who choose to follow a delayed antibiotic strategy for children participating in the RCT or OCS will be asked to give parents clear advice with regard to cashing in and using the delayed prescription. Parents will be advised to wait before giving any delayed antibiotics to their child as per NICE guidelines. For children recruited to the OCS and for whom the clinician has prescribed a same day antibiotic, standard advice about the use of same day antibiotics will be provided as per NICE guidelines and the clinician's routine practice.

### 9.9. Advice to parents on rescue analgesia

The child's Responsible Clinician will advise the parent on the appropriate use of paracetamol and/or ibuprofen and/or other pain-relieving therapies as per their routine practice.

Clinicians will be provided with cards detailing the standard advice about delayed antibiotic use and the use of rescue analgesia, which can be given to participating parents.

### 9.10. Training parents in how to administer the ear drops, including vigilance for possible tympanic membrane perforation

The Responsible Clinician will explain, to parents of children allocated to one of the two treatment (ear drops) arms of the RCT, how to administer the drops to their child. Parents will also be provided with printed instructions, within the Patient Pack, and a training video will be made available on-line.

Using our PPI representatives to inform the final wording, we will draw parents' attention to being vigilant for any new discharge from the child's ear, especially a discharge that contains pus, is yellow/green or has a bad odour. This should result in further drops being withheld.

### 9.11. Training parents in how to complete the follow-up

The Recruiting Clinician will take the daily Symptom and Recovery Questionnaire from the Patient Pack and label it with the child's Participant ID number and associated password (provided in the Patient Pack, with the Participant ID labels, for parents who wish to complete the diary online) and write in the recruitment date and the dates / times on which the parent is requested to complete the diary during the remainder of the day of recruitment, and during the succeeding seven days. The Recruiting Clinician will explain to the parent how to complete the diary, including daily recording of:

- The number of doses of trial ear drops administered (for parents whose children are given ear drops only);
- The number of doses of rescue analgesia (paracetamol and/or ibuprofen and/or other pain-relieving agents) given to the child orally;
- The number of doses of antibiotics given to the child (if the child has been given same day or delayed antibiotics);
- How to report the parent-rated child's daily pain score (as an average of the child's perceived pain over the preceding 24 hours);
- For children of 5 years or above, how to ask the child to score their ear pain and to administer small rewards (to be decided in consultation with our PPI representatives) for doing this;
- How to score the child's symptom burden;
- How to report any time taken off work, or time missed from nursery, childcare or school;

The Recruiting Clinician will explain to the parent that they will be contacted by a member of the study team as soon as possible, ideally that same evening, to support them with the completion of the daily diary. The Clinician will be asked to make the parent aware that the caller will be one of the named staff pictured on the PIS, and ask the parent to key in the CEDAR study mobile telephone number to their mobile phone (named as 'Ear Pain Study') so that they will not receive a call from an unknown source. The Recruiting Clinician will also explain to the parent that the study team will contact them at least four times during the next seven days to ask about their child's progress and to help them to complete the whole diary. The Recruiting Clinician will also explain that the study team will provide the parent with complete instructions and support regarding what to report each day, to reassure the parent and to reduce their information burden.

### 9.12. Entry of recruitment data to online CEDAR clinical database

Following recruitment, the Recruiting Clinician will enter all of the baseline recruitment data onto the web-based trial database, except for consent and participant registration data (which will be sent by secure fax to the local trial centre by the end of the day, and which will also be posted direct to the trial centre). The remaining baseline CRF data will be entered by the Recruiting Clinician (or by the research nurse or other member of appropriately qualified and trained personnel to whom the data entry is delegated) within 24 hours of recruitment. Clinicians will have the facility to enter the child's baseline data directly online if that is more convenient to them. Clinicians who find it more convenient to complete paper CRFs will be provided with paper documentation and asked to enter the data onto the validated online clinical database within 24 hours of recruitment.

### 9.13. Updating of child's electronic medical record

Once the entry of the child's baseline recruitment data is complete online, the database will provide a textual summary of the eligibility data, relevant clinical observations, relevant symptoms and signs, working diagnosis, prescription of trial medicines (if the child has been allocated to one of the two treatment arms of the RCT) and any antibiotics, the child's Participant ID and date of recruitment. This summary will be suitable for cutting and pasting directly into the child's electronic medical notes and will be tested for compatibility with EMIS, EMISWeb, SystmOne, Vision and any other electronic health record systems in use by participating primary care sites.

### 9.14. Notification of recruitment to the study team

The final task for the recruiting site in each recruitment process is to notify the study team that the child has been recruited with the informed consent of the parent or carer. The process by which this will be done for CEDAR will be one that has been successful and effective in a previous clinical trial. The site will send to the secure study fax machine (which is kept on over 24 hours), by the end of the same working day as recruitment, a copy of the child's baseline registration data (name, parent's name, parent's telephone contact details and preferred time of day for making contact) and a copy of the completed consent form initialled and signed by the parent and signed by the Recruiting Clinician. The fax transmission of these two key documents provides the signal to the trial team to initiate parent contact and to start the follow-up process. Following the secure fax, these two documents will be sent to the trial centre by post, using a pre-paid return envelope, within 24 hours.

Separate notification arrangements will be made for recruitment from the Bristol CED, in line with the Trust's current practice.

### 9.15. For children recruited at CED, WIC or OOH sites: informing the child's GP

For children visiting the Children's Emergency Department of Bristol Royal Infirmary (University Hospitals Bristol NHS Foundation Trust), an email is routinely sent to the child's registered GP and Health Visitor to inform them of the visit, clinical diagnosis and treatment given. For children recruited to CEDAR at the Bristol CED, the cut-and-paste CEDAR clinical database output summary will be pasted into this report before sending, to alert the GP that the child has been recruited.

To ensure that the child's GP is fully informed about the trial, for all children recruited at a primary care site which is not their regular practice (i.e., for children recruited at CED, WIC or OOH sites) the study team will send to the child's regular GP, on the day of recruitment or first thing the following morning, a standard, ethically approved letter giving details about the research and confirming the date on which informed consent was given for the child to take part in the research.

### 9.16. Maximising retention

The trial will employ an experienced, full-time Trial Research Nurse in order to conduct the follow-up telephone calls to parents and to ensure that all parents receive adequate support during the follow-up period. We are aware that some parents (e.g. new parents, single parents and parents in the 'no drops' group) may find it more challenging to complete the trial. Providing additional Trial Research Nurse exclusively for these parents, however would bias the intervention, and it is also important (for economic data accuracy and the child's healthcare) that the study team is not seen as an alternative to the child's GP. Any trial queries will be addressed by a member of the team, usually a nurse, but nurses will be careful to refer health queries to the appropriate health provider. In order to inform our recruitment and retention strategies we will, through our PPI activities, draw on the experience of parents whose child has had AOM. Furthermore, the qualitative study will investigate parents' views and experiences of the diagnosis and treatment of AOM in the CEDAR trial.

### 9.17. Symptom and Recovery Questionnaire completion and telephone follow-up Days 1-8

Parents will be asked to complete a Symptom and Recovery Questionnaire for the day of recruitment (Day 1) and for the succeeding seven days (Days 2-8). To support this Symptom and Recovery Questionnaire completion and to secure the highest achievable rates of primary outcome data capture, parents of children recruited to the study will be telephoned (using their preferred telephone number, and at a time convenient to them) at the following time points. Each telephone call apart from the final (Day 8) call is anticipated to take up to 15 minutes, but this could be longer if the parent has many questions or wishes to discuss aspects of their child's progress or the research. The Day 8 call is anticipated to take up to 20 minutes, as additional health economic questions will be asked. Telephone calls will be made Monday to Friday, and calls relating to weekend time points will be made as close as possible to the time point, on the preceding Friday or following Monday.

**Day 1 (the day of trial entry):** parents will be telephoned as soon as possible after recruitment by the Trial Research Nurse or another member of the study team. The Research Nurse / research team member will thank

the parent for entering the study, ask them if they have understood everything they have been asked to do by the GP, and ask them if they have any further questions. The Nurse will explain to the parent that they should complete the diary for today and for the following seven days. The Nurse will then guide the parent through the first day's (Day 1) data collection within the Symptom and Recovery Questionnaire and record the information collected over the telephone on a copy of the paper Symptom and Recovery Questionnaire (the 'office use' version) to guard against the potential loss of data. The baseline information collected on Day 1 via the Symptom and Recovery Questionnaire will be as follows:

- Child's quality of life over the previous 3 months using the OMQ-14 validated questionnaire (the questionnaire is completed at this point in order to reduce the pressure on recruitment within the GP consultation);
- Baseline sociodemographic factors: parental occupation, child's ethnicity, maternal smoking habits, number of other children in the child's home, and whether the child was breastfed at 3 months (the rationale for collecting these data at this point is also to reduce the pressure on recruitment within the GP consultation);
- The child's daily parent-rated ear pain score (average over the preceding 24 hours);
- Children aged five years and above will be asked to rate their own ear pain;
- Presence of any ear discharge (if yes, parent will be advised to stop using ear drops immediately);
- Number of doses of ear drops administered, and to which ears;
- Whether the child has taken any antibiotics by mouth today;
- Number of doses of rescue analgesia administered;
- Parent's rating (mild, moderate or severe) of the child's other symptoms over the preceding 24 hours, including: episodes of distress or crying; disturbed sleep; interference with normal activities of daily living; eating or drinking less than normal; fever; hearing problems; any other symptoms (potential adverse events);
- Has the child missed any school, nursery or childcare today
- Has the parent or carer lost time from work today

On the Day 1 telephone call, the Research Nurse will remind the parent to complete the CHU-9D quality of life questionnaire for their child on the following day, at 24-36 hours post recruitment – i.e. on Day 2.

**Days 2-7:** parents will receive another two calls, at their convenience, to support them in completing the first week of the daily Symptom and Recovery Questionnaire. The calls will guide the parent through the daily Symptom and Recovery Questionnaire and transcribe the data collected over the phone onto the 'office use' shadow Symptom and Recovery Questionnaire at the trial centre. The information for which the Nurse will ask the parent for each day is as follows:

- **Day 2 only:** Child's quality of life over the previous 24 hours using the CHU-9D validated questionnaire;
- The child's daily parent-rated ear pain score (average over the preceding 24 hours);
- Children aged five years and above will be asked to rate their own ear pain;
- Presence of any ear discharge (if yes, parent will be advised to stop using ear drops immediately);
- Number of doses of ear drops administered (up to a maximum number of 8 days), and to which ears;
- Whether the child has consumed any antibiotics by mouth today;
- Number of doses of rescue analgesia administered;
- Parent's rating (mild, moderate or severe) of the child's other symptoms over the preceding 24 hours, including: episodes of distress or crying; disturbed sleep; interference with normal activities of daily living; eating or drinking less than normal; fever; hearing problems; any other symptoms (potential adverse events);
- Has the child missed any school, nursery or childcare today
- Has the parent or carer lost time from work today

**Day 8:** parents will receive the final telephone call to support the completion of the 1-8 day Symptom and Recovery Questionnaire. As well as the daily data items listed above, the following data items will be requested on Day 8:

- Child's quality of life over the previous 24 hours using the CHU-9D validated questionnaire;
- Visits to GP, WIC or OOH during the preceding 7 days (i.e. the 7 days after the day of randomisation)
- Use of hospital-related services including CED during the preceding 7 days

- Use of NHS telephone service 111 (or equivalent) during the preceding 7 days
- Use of prescription medicines during the preceding 7 days
- Purchase of over-the-counter medicines during the preceding 7 days

**9.18. Parental beliefs and opinions**

- Overall, how satisfied were you with the treatment your child received for their ear pain?
- If ear drops were to become available as an over-the-counter medicine, would you use them to treat your child's ear pain?
- Has taking part in the CEDAR study changed the way you would treat your child if they should develop another ear infection in the future?
- Parent's belief in likely benefits of antibiotics: "What medicine would you want to use for your child if s/he had a similar illness in the future?

The following questions will also be asked of parents participating in the 3 arm main trial only:

- Do you think your child was given active ear drops or placebo ear drops?
- Once the trial is finished, would you like to know whether your child received the active or placebo ear drops?
- If yes, do you give your permission for us to inform you GP practice which ear drops were allocated to your child?

**9.19. Ear symptom resolution**

- Is your child's ear pain better?
- Does your child still need to take any medicines for pain or fever?
- If the child's ear pain is ongoing at seven days, we will ask parents' permission to continue to contact them by telephone, twice weekly (for a brief interview and with no further paperwork) until the child is free of ear pain and without medications for two consecutive days.

The names and contact details of the members of the study team will be included in the PIS. Parents will be able to contact the study team if they have any queries about the follow-up.

To thank them for their time and contribution to the research over the last week, parents will be sent a £5 High Street Shopping voucher following the completion of the day 7 telephone interview.

**9.20. Telephone follow-up post Day 8 (for children with ongoing ear pain)**

For children whose ear pain is still rated by the parent at >0 after seven days post-randomisation, we will ask the parent's permission to continue to contact them by telephone twice weekly until the child's ear pain resolves (i.e. until the child is free of ear pain for two consecutive days without medication), of which one call at the end of that week to ask them about their healthcare resource use during the week.

These calls will take place for each week during which the child has experienced ongoing ear pain and until illness resolution (i.e. for ear pain ongoing after Day 8, up to Day 15; for ear pain ongoing after Day 15, up to Day 22, etc) up to a maximum of four weeks. We anticipate that the 'additional' mid-week telephone interview is anticipated to take no more than 5 minutes per week, and the additional end-of-week telephone interview will last no longer than 10 minutes. We anticipate that these 'additional' telephone interviews will be conducted in around 10%17 of children taking part in the study.

The purpose of the mid-week telephone interview, until the child's ear pain resolves, will be to ask the parent:

- The child's parent-rated ear pain score at the point of the telephone call (average over the preceding 24 hours);
- Number of doses of ear drops administered, and to which ears;
- Whether the child has consumed any antibiotics by mouth today;
- Number of doses of rescue analgesia administered.

- Collect resource use data (once at the end of the week).

At the end-of-week telephone call the parent will be asked about the family's use of healthcare resources as a result of the child's ear pain, including:

- Visits to GP, WIC or OOH
- Use of hospital-related services including CED
- Use of NHS telephone service 111 (or equivalent)
- Use of prescription medicines
- Purchase of over-the-counter medicines
- Loss of parent or carer's time from work
- Loss of child's time from nursery, childcare or school

IF the ear pain stops before or by the mid-week phone call, then the resource use questions due at the end of week phone call can be asked as a round up at the mid-week call to avoid calling parents again whose children are now well. In other words, we will ask them what resources they have used as a round-up UP TO the point in the week when the ear pain stopped (as long as that is by the time of the mid-week call).

The parent who has agreed to let the study team continue to contact them will be asked for this information over the telephone, and will not be expected to complete any further Symptom and Recovery Questionnaire, either paper or online.

### 9.21. Three month Quality of Life postal questionnaire

After three months we will send parents (or email, depending on their preferred mode of communication) a Quality of Life Questionnaire which will contain the CHU-9D and the OMQ-14 validated questionnaires. Parents receiving the postal version will also be sent prepaid return addressed packaging for the return of the paper questionnaire to the study team.

In order to keep parents informed of the forthcoming questionnaire, we will telephone or email them (depending on their preferred mode of communication), sending a short, standard message two weeks before the postal or online questionnaire is sent out to let the parent know that they will be receiving it on or around a specific date.

## 10. DATA COLLECTION

### 10.1. Justification for quantitative data collection instruments

***Antibiotic consumption***

Since our work has shown that any (vs. no) antibiotic use is known to influence antimicrobial resistance,[10] we will record the use of any antibiotics by mouth in the 7 days following randomization (where Day 1 is the day of randomization, and Day 8 is the seventh day after the day of randomisation). We will also record the number of doses of antibiotics given in the first 7 days post randomisation (Symptom and Recovery Questionnaire), the type of antibiotic prescribed (baseline Case Report Form and primary care notes review), and the dose and number of days for which the antibiotic was prescribed (primary care notes review).

***Child ear pain***

We have used the PeDIMMPACT (Paediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) recommendations[13] in selecting the zero to ten pain numerical rating scale (used in our previous trial[6]) for our primary outcome. Although no parent completed pain score for younger children can completely overcome the challenge of differing parental and child pain perceptions, this scale has been shown to be valid and sensitive to change across the full trial age group, provide a global measure of pain for a 24 hour period (which is reflected

in the eligibility criteria and therefore does not restrict recruitment to pain scores within specified time periods), and in combination with our other outcomes, meet the PeDIMMPACT recommendations.

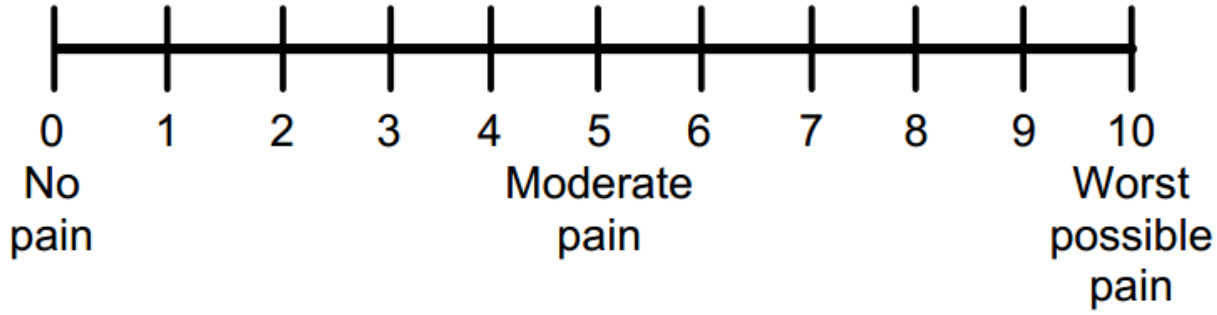



***Figure 8.1.1: the 0-10 Numeric Pain Rating Scale***

To complement this, and in order to measure any potential difference in parent and child pain perception, we will ask children aged ≥5 years to record pain using the Faces Pain Scale – Revised (FPS-R) which also rates pain zero to ten.[14]

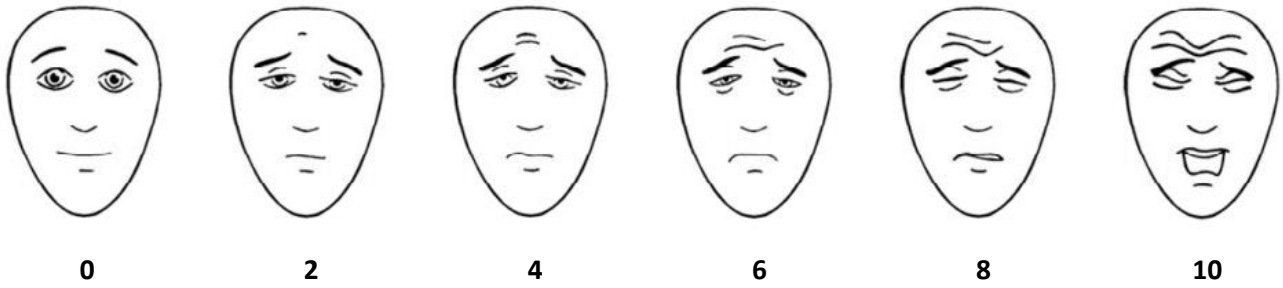



***Figure 8.1.2: the Faces Pain Scale – Revised (FPS-R) [Hicks et al 2001]***

The Faces Pain Scale – Revised (FPS-R) was selected as the trial's self-report measure of pain intensity for children who are old enough to score their own pain (5 years and above), as the problem of confounding the faces at either end of the scale with emotional states was less likely than with the Wong-Baker FACES pain scale [Stinson et al 2006] which is extensively used in clinical practice.

We are aware that the majority of the children recruited to CEDAR will be too young to be able to self-report their ear pain, and that the FPS-R is not validated for use in such children, for whom behavioural observational scales are recommended (e.g. the FLACC scale [Merkel et al 1997]). A behavioural observational score, however, cannot be considered to be equivalent to a 0-10 parent-rated pain score or a 0-10 FPS-R self-score (for children aged 5 or above). Furthermore, the behavioural observational score could only be completed by the parent, from whom we are already requesting their perceived child ear pain rating on the 0-10 numeric scale.

We will collect both parent and child pain scores where possible, at presentation, after presentation (as close as possible to 60 minutes after giving the first dose of the ear drops, a time point informed by feedback obtained from our PPI representatives) and on the evening of Day 1, and all following evenings "at the end of the day" (recording the time they do so also). Pain is mostly worse in the evening/night therefore collecting this data in the evening when the symptom is likely to be peaking is sensible.

We will ask parents (and children) to record pain bearing in mind that the parent score, as stipulated in the diary, will reflect pain over the previous 24 hours, but the child score will reflect the pain now. To fully interpret the latter, we will therefore also need to record the timing of drops, paracetamol, ibuprofen and other pain-relieving therapies.

***Other symptoms***

Other symptoms will be measured using a validated[51] Symptom and Recovery Questionnaire, as per our other paediatric studies.[6 52]

***Preference based quality of life***

There is currently no single valid preference based measure of utility (for calculating QALYs), that can be used in children from age 12 months to 10 years. Most generic measures (e.g. HUI3, EQ-5D Y, CHU-9D) are not designed for or validated in pre-school (i.e. the majority of children in CEDAR). The CHU-9D data, for example, is a preference-based instrument that can be used for QALY calculation in school aged children (7-10 years).

Therefore, we propose a dual approach: parents of all children aged 2 and older will be asked to complete the disease specific OMQ-14[19] at baseline and 3 months, for ear problem related quality of life. The OMQ-14[19] is a subset (14 of 30 items from the OMQ30) and has been successfully used in previous[53] and the current HTA funded 'AIRs trial' (PI Williamson for both trials). Parents of school aged children (≥5 years) will also be asked to complete the generic CHU-9D[18] preference measure at baseline, 24 hours, 7 days and 3 months after randomisation. As a preliminary secondary analysis, which would allow some comparison with other interventions, the CHU-9D data and multiple imputation will be used to calculate QALYs for those children outside the 7-10 year age range.

### 10.2. Summary of quantitative trial data collection

Day 1 (baseline data collection collected by Responsible Clinician at the index consultation) will include: eligibility criteria; age; gender; postcode; parent telephone number; summary of symptoms (including pain score); clinical examination findings; significant co-morbidities; clinician diagnosis; CHU-9D and OMQ-14. The Trial Nurse will try to make contact on Day 1 to address any questions or concerns about the trial. The Patient Pack will contain a £5 voucher to thank parents for helping with baseline data collection.

Days 1 to 8 (Symptom and Recovery Questionnaire supported by Trial Nurse telephone call) will include daily: global measure of pain numerical rating score (*key secondary outcome at 24-36 hours*); symptom burden; CHU-9D (Day 1 and Day 2); adverse events; antibiotic doses, ear drop and other analgesic use. As per previous studies,[52] parents will be asked to record these until two days of symptom resolution, which for AOM is thought be eight days (for 90% of children).[17]

Day 8 (Symptom and Recovery Questionnaire supported by Trial Nurse/Administrator telephone call) will include antibiotic consumption (*primary outcome*) and daily: pain scores; symptom burden; adverse events; ear drop and other analgesic use; CHU-9D; NHS contacts; days off school/nursery; carer lost productivity and other expenses. The Trial Nurse/Administrator will also ask parents, at the Day 8 telephone call, about: carer opinion of, and satisfaction with, treatment allocation, intention to purchase drops if available OTC, their beliefs about the likely benefits of antibiotics, and ask the parent to return: (i) the ear drop bottle with any unused drops, and (ii) any used antibiotic packaging with unused antibiotics, in pre-paid, pre-addressed protective envelopes. The ear drop bottles will be weighed on receipt as a measure of trial medication adherence. The study team will send the parent a £5 voucher on completion of the Symptom and Recovery Questionnaire.

Post Day 8 (Trial Nurse/Administrator telephone call): Parents whose children are still experiencing ear pain ~~at~~ after 7 days following the day of randomisation will continue to be telephoned twice weekly in order to identify the date on which the child's parent-reported ear pain had resolved for two consecutive days, without analgesic medication. We estimate that 10% of children will still be symptomatic at this point (Day 8)[17]. Parents will be asked to score their child's ear pain (on average over the preceding 24 hours) and to report any oral antibiotic or analgesic consumption.

Month 3 (primary care notes review and postal/ telephone questionnaire) will include: primary care notes review for primary and secondary care attendances, and Serious Adverse Events and a postal/telephone questionnaire to collect CHU-9D and OMQ-14, following which the study team will send the parent a £5 voucher.

### 10.3. Observational study data collection

Data collection for the observational study will be exactly the same as for the trial, with the exception of questions about use of ear drops.

### 10.4. Qualitative data

All interviews will be conducted by telephone. At interview, participants will be asked to give verbal consent, following which a flexible topic guide will be used to ensure primary issues are covered during all interviews, but without dictating data collection, allowing participants to introduce unanticipated issues. Topic guides will be modified as necessary to reflect emerging findings. The researcher will use open-ended questioning techniques to elicit participants' experiences and views of key events and participants will be asked to provide examples. Interviews with health care professionals are expected to last around 30 minutes and interviews with parents' around 45 minutes, and will be recorded using a digital voice recorder, transcribed and anonymised to protect confidentiality. Parents who take part in interviews will receive a £10 High Street voucher.

As well as parents participating in the RCT, we will also endeavour to conduct qualitative telephone interviews with parents who have declined RCT participation, and with parents who have chosen to withdraw (n=10).

## 11. ASSESSMENT OF EFFECTIVENESS

***Primary outcome***

1. Any antibiotic consumed by Day 8 (measured using daily Symptom and Recovery Questionnaire with telephone support calls during week 1), where Day 1 is the day of randomisation;

***Secondary outcomes***

**[Key secondary outcome]**

2. Ear pain over first 24-36 hours post randomisation using the parent completed, validated numerical rating scale successfully used in our previous trial[6] (Symptom and Recovery Questionnaire with telephone support call in first three days).

**[Other secondary outcomes]**

3. Time taken before antibiotics started (Symptom and Recovery Questionnaire with telephone support calls during week 1);
4. Daily symptom severity (until illness resolution i.e. child free of ear pain without need for rescue analgesia for two consecutive days, expected by 8 days for most children[17]) including episodes of distress/crying, disturbed sleep, interference with normal activity, appetite, fever and hearing problems (Symptom and Recovery Questionnaire, supported by telephone calls);
5. Child completed Faces Pain Scale-Revised (FPS-R [Hicks et al 2001], for children aged ≥5 years) (Symptom and Recovery Questionnaire);
6. Adverse events (Symptom and Recovery Questionnaire, supported by telephone calls);
7. Ear drop and rescue analgesia consumption (Symptom and Recovery Questionnaire, supported by telephone calls);
8. Parent satisfaction with, and opinion of, treatment allocation and future intention to use drops (with/without prior GP consultation if drops were to become available over-the-counter) after 7 days (Symptom and Recovery Questionnaire, with telephone support call at one week);
9. Preference based quality of child life measured (baseline, 24-36 hours, 7 days and 3 months post randomisation) using CHU-9D[18] for children age ≥5 years (CRF, Symptom and Recovery Questionnaire supported by telephone calls, and postal/online questionnaire at 3 months)
10. NHS costs up to 7 days after randomisation (Symptom and Recovery Questionnaire, supported by telephone call at one week) and contacts to 3 months (primary care medical notes review);

11. Child's school/nursery absences, parent lost productivity and other expenses up to 7 days after randomisation (Symptom and Recovery Questionnaire, supported by telephone calls)
12. Child's quality of life (OMQ-14,[19] for children aged 2 years and older) at baseline and 3 months after randomisation (CRF and postal/online questionnaire at 3 months).
13. Qualitative outcomes to assess acceptability, barriers and adherence, a purposeful sample of parents and clinicians will be asked to participate in qualitative interviews to explore experiences of, and attitudes to AOM and its treatment.

## 12. ANALYSIS

### 12.1. Sample size calculation

***Antibiotic consumption (primary outcome)***

Current United Kingdom (UK) antibiotic prescribing rates are high for children with AOM, in fact higher than for any other respiratory infection of childhood.[8] One study showed prescribing rates of 84%,[9] while another showed three-quarters of UK general practices prescribe antibiotics to at least 80% of children with AOM.[8] We are not aware of any evidence to inform consumption rate, but our clinical experience and PPI group suggest that the majority of parents will give their child a prescribed antibiotic. Our power calculation therefore (conservatively) assumes a no drop (usual care) arm antibiotic consumption rate of 80 to 90%. While it is agreed that for reducing the development of antimicrobial resistance, antibiotic *consumption* is more meaningful than *prescribing*, there is no agreed minimum difference in antibiotic consumption worth detecting. Our work has shown a clear and prolonged link between primary care prescribed antibiotics and antimicrobial resistance lasting over 6 months,[10] and although we did not find evidence to define a clinically important difference in consumption rates, these data[10] suggest that a 20% change in consumption could have important effects on antimicrobial resistance, both in children and in their infectious contacts. Assuming a Type II error rate of 0.1 (90% power) and Type I error rate of 0.05 (alpha) the number of children needed in each group (active eardrops and no drops) ranges from 92 to 119 to demonstrate a 20% fall in antibiotic consumption from 80-90% in the control group to 60-70%. Using the more conservative estimate of 119, and taking into account 20% attrition, this would give a final sample size of 149 per arm.

***Pain (secondary outcome)***

The pain the child suffers is an important outcome for parents and will be a key secondary outcome, comparing whether the active drops are more effective than placebo drops. We will measure pain using the validated zero to 10 numerical rating scale we used in our previous RCT of delayed vs. same day antibiotic for childhood AOM.[6] This trial showed mean pain scores of around 6.5 (same day antibiotics) and 5.5 (delayed) at 24 hours and overall mean pain scores of 2.6 (same day) and 3.6 (delayed). Regarding the minimum clinically important difference, our PPI group indicated that they would find a 10% (or greater) reduction in pain useful, and the largest difference observed in our previous trial using the same Symptom and Recovery Questionnaire was one point [Little BMJ 2001]. Again assuming 90% power and $\alpha$=0.05 we can detect a mean difference of 1 (SD=2.5 based on trial data) in pain score between the active and placebo ear drop groups, with 133 children per arm. Assuming 20% attrition and equal numbers in the three groups, we need 167 children per arm of the trial (more than for the primary outcome) and therefore 501 children in total.

### 12.2. Sampling

***Trial***

Children will be recruited from primary care where the vast majority of children are managed. Selection bias will be minimised by encouraging recruiting sites to invite consecutive eligible patients and measured by asking them to record the characteristics of patients/reasons where this is not possible. Children not eligible for the trial or whose parents decline participation in the RCT will be invited to participate in the OCS.

Previous studies suggest 80-90% of children with AOM use antibiotics. The primary outcome of the study is to reduce antibiotic use in this group to 60-70%. Assuming 90% power and alpha set at 0.05 between 109 and 121 children would be needed in each of the active ear-drop and no-drop groups to detect a 20% reduction. As a key secondary outcome we are also interested in measuring whether the active eardrops reduce pain compared to the non-active ear-drops. Again using 90% power and alpha set at 0.05 a difference of 1.0 on the pain numerical rating scale (using an SD of 2.5 from our previous RCT suggests we need 133 children in each of the active and placebo ear drop groups. Thus using this slightly larger number of 133 children for all three groups and assuming no more than 20% attrition, we need to recruit 167 children per arm of the trial or 501 children in total.

A decision will taken as to whether children recruited during the initial 2 arm pilot (for the first 3 months, prior to the introduction of the delayed placebo) can be included in the analysis of the full 3 arm trial, following a review and comparison of the data collected under the two different randomisation schedules.

***Observational cohort study***

The observational study will have the similar, but slightly broader inclusion criteria and will be straightforward for patients who do not wish to participate in the trial because it will not involve any intervention. Participation in the observational study will simply involve completion of baseline and follow-up data collection instruments. For children whose parents do not wish them to be in the observational study, we will ask clinicians to record anonymous characteristics (gender, date of birth) and reasons for non-participation where possible. All site communications will emphasise the importance of recruiting to the trial over the observational study and sites will be limited to a trial:observational study recruitment ratio of 1:1 (this is higher than the ratio observed in one of our previous trials of antibiotics for adult chest infections in which the same ratio was approximately 2/3:1/3).

***Qualitative study***

Purposive sampling will attempt to capture maximum variation in views and experiences in order that they adequately reflect those of a range of parents with children with newly diagnosed AOM and health care professionals involved in their care. All parents agreeing to participate in the trial will be asked, at the time of consent, if they are willing to be contacted about taking part in a qualitative telephone_interview (see CEDAR participant and data flow diagram). From willing participants, a purposive sample will be drawn in relation to: (i) trial Centre (Bristol, Southampton, Cardiff); (ii) trial arm (active, placebo or no drop); and (iii) socio-demographic factors including child's age, ethnicity and socio-economic status (with participants being selected from areas of high and low social-economic deprivation, based on Index of Multiple Deprivation score).[50] In addition, telephone interviews will be conducted with a sample of parents that declined trial participation. Health care professionals (GPs, NPs, and ED doctors and nurses) involved in the trial will be purposively sampled in relation to: (i) trial Centre; (ii) type of primary care site (GP practice; Walk-in and Out of Hours Centres; Emergency Departments); and (iii) length of time since qualification. Sample sizes will be determined by the need to achieve data saturation, such that no new themes are emerging from the data by the end of data collection.[45] Interviews will be analysed in batches, and sampling will continue until no new themes are emerging. This is likely to include up to 25 health care professional and 30 parent interviews and 20 telephone interviews for those that declined trial participation or withdrew from the trial.

### 12.3. Randomisation

***Blinding of participants***

The participants will be blinded to the trial in that only one third will be aware that they are in the usual care group. We will present this arm of the trial to parents as "one of the three treatment paths within the trial to which children will be randomised", rather than as "the control arm".

During the initial 2 arm pilot period, parents and clinicians will be aware that treatment allocation is either to the active treatment arm (active ear drops and usual care) or to the usual care/no ear drops ("control") arm.

***Blinding of recruiting clinicians***
The randomisation process will ensure that that there is no opportunity for clinicians to influence which child is allocated to which treatment. Clinicians recruiting children to the trial will be blinded until after treatment allocation. Once written informed consent has been obtained, the parent will be given a Patient Pack which will be identical across all three arms. Once the pack is opened during the consultation, the clinician and parent will learn whether or not the child has been allocated to one of the ear drop arms – but will remain blinded to allocation between the active and placebo drops.

For children recruited within the initial 2 arm pilot period, allocation to the active treatment arm (active ear drops and usual care) or to the "control" arm (usual care/no drops) will be known by the clinician and parent at the point of recruitment, following the eligibility assessment and informed consent processes.

***Stratification***
We will stratify by centre so that the distribution of the three arms are fairly equal between Bristol, Cardiff and Southampton. We will use sites' proven record of recruitment to previous studies to inform the distribution of recruitment packs at start-up.

***Block size***
We will randomise in batches of 30 within which treatment allocation will be equal (10:10:10) (for the initial 2 arm pilot, treatment allocation will also be equal (10:10)). We will closely monitor the recruitment at each centre, and adjust the ratio of the number of blocks provided to primary care sites within each trial centre to ensure they receive patient and medicine packs in proportion to their rate of recruitment.

### 12.4. Minimising bias
Participants in clinical trials frequently differ from the general population with the condition of interest, and it can be a challenge to determine the degree and likely effects of any selection bias. In addition to trying to minimise selection bias by encouraging practices to recruit sequential eligible children and making the trial relatively straightforward to take part in, we will seek to measure selection bias, model the effects of any selection bias, and provide data on the presentation, management and outcomes of children with AOM who are not recruited into a trial, by conducting the observational study of children who are not recruited into the trial.

### 12.5. Statistical analysis

***Quantitative analysis***
The analysis and presentation of the trial will be in accordance with the CONSORT guidelines and a full analysis plan developed. Descriptive statistics will be used to assess balance in the randomised arms at baseline and will be presented as means and standard deviations for normally distributed variables, medians and inter-quartile ranges for any skewed variables, or numbers and percentages.

The first part of the primary comparison will be the prevalence of antibiotic use at Day 8 post consultation (where Day 1 is the day of randomisation) between those children receiving active eardrops and those receiving no drops (usual care) and will be analysed on an intention to treat basis. The time between consultation and antibiotic consumption will also be explored. Logistic regression will be utilised and the findings adjusted for marked imbalance at baseline (e.g. that differ by more than 0.5 standard deviations for age or univariable significant differences in proportions such as those with bilateral AOM). Post randomisation health care related variables such as other analgesics taken by the child (we will record the timing of the last dose of oral analgesics given to the child that day, prior to the daily parent-rated child ear pain score) will not be adjusted for in the main model but will be mediated for in a secondary analysis. For any continuous outcomes that are clearly non-normally distributed, appropriate transformations will be documented and justified in the model. To assess the potential effects of missing data, multiple imputation methods will be utilised in a sensitivity analysis.

The key secondary analysis will analyse the difference in pain scores, between the active and placebo groups, 24-36 hours after administration of drops. This information will be collected using the Symptom and Recovery Questionnaire by asking the parents to score their child's ear pain over the past 24 hours on the evening of Day 2. The analysis–will be conducted using linear regression, adjusting for baseline pain score (collected prior to randomisation) and centre. This will be followed by a linear regression model where all other principles described for the primary analysis above will be applied, including the potential mediating effect of antibiotic use and other analgesics on how this might affect the interpretation of the results. Other secondary analyses will use the appropriate regression method, and, as these will be exploratory in nature, the p-value will be presented but will interpreted with due caution. The analysis will be conducted using the statistical package STATA. The trial statistician and senior statistician will be blinded to the different arms of the trial for the main analysis.

At the pre-funding stage, two reviewers identified that the use of antibiotics and analgesics could influence the effect of the ear drops on pain. Although evidence suggests the effects of antibiotics are modest [Little BMJ 2001], on consideration we agree and will not adjust for post-randomisation health care variables such as analgesics and antibiotics in our main models or when reporting our main results. However as part of secondary sensitivity analyses, we will look at the mediating effect of analgesics and antibiotics to help interpret and contextualise our main findings, with the potential for confounding kept in mind.

We will measure selection bias, model the effects of any selection bias, and provide descriptive data regarding the presentation, management and outcome of children with AOM who are not recruited into a trial. We found evidence that fewer than 44% of eligible children were recruited into AOM trials [Bains 2001] and that the most likely reason for not recruiting was severity. To test this within CEDAR and to inform the assessment of generalisability, we will compare the global illness severity scores, made by parents and clinicians at baseline, across the RCT and OCS.

A full Statistical Analysis Plan will be developed and reviewed by the Trial Steering Committee.

***Health economic analysis***

The economic analysis will consist of a cost-effectiveness analysis and cost consequence study. As antimicrobial resistance is such an important concern, we propose a cost-effectiveness analysis with antibiotic use as a proxy for this outcome as our primary economic analysis. The cost-consequence study (including quality of life) is a secondary economic analysis.

The primary economic analysis will take a societal perspective including costs to the NHS and the family. Our sample size calculations are based on the primary outcomes (antibiotic use and ear pain). Avoidance of antibiotic prescriptions is a key economic outcome because of the large intangible costs of antibiotic resistance.[56] The economic case for or against the active intervention is most likely to hinge on externalities (i.e. antibiotic use and resistance) in the population, rather than purely within trial estimates of costs and quality of life, therefore powering the economic analysis based on trial cost-effectiveness would provide too narrow a focus. The primary comparison will be the cost per antibiotic avoided during the acute episode between those children receiving active eardrops to those receiving no drops (usual care) and to those receiving placebo drops. The incremental NHS treatment costs (i.e. initial ear drops plus antibiotic prescriptions and other health service contacts) during the first 7 days after randomisation will be ascertained from the Symptom and Recovery Questionnaire and Day 8 telephone call and valued using national unit costs.[54 55] Opportunity costs to parents (i.e. lost work days, out of pocket expenses) and children (school absences) will be measured at the Day 8 telephone call, and valued using human capital and shadow price approaches.

Bootstrapping will be used to calculate confidence intervals around the point estimate of the incremental cost-effectiveness ratio and cost-effectiveness acceptability curves. We will investigate the effect of any differences in baseline characteristics and if necessary will use regression techniques to adjust for these. To assess the potential effects of missing data, multiple imputation methods will be utilised in a sensitivity analysis.

In the secondary economic analysis we will conduct a cost consequence study tabulating 3 month societal treatment costs (including data from the 3 month questionnaire and GP note review) alongside other important outcomes including 24-36 hour ear pain relief, overall symptom burden, acute illness duration (the end of which will be defined as the last day post randomisation on which parent-reported child ear pain scores zero for two consecutive days without other analgesic medication), CHU-9D utilities (in school aged children, and through multiple imputation to children outside this age range) and OMQ-14 quality of life scores.

Our study will provide decision-makers with an estimate of any incremental costs of the active intervention and any benefits in terms of reduced antibiotic prescriptions, reduced symptoms and improved quality of life. If the active intervention does reduce antibiotic use without a detrimental impact on symptoms, we will discuss the implications for parents and the NHS of making the drops available over the counter (this will be explored through the qualitative interviews). We envisage this to be part of drawing policy implications from our findings, rather than a formal extrapolation model.

A full Health Economics Analysis Plan will be developed and reviewed by the Trial Steering Committee.

***Qualitative analysis***

Interview transcripts will be checked for accuracy and then imported into NVIVO qualitative data analysis software, to aid management and indexing of data. Analysis will begin shortly after data collection starts, will be ongoing and iterative. Analysis will inform further data collection: for instance, analytic insights from data gathered in earlier interviews will help identify any changes that need to be made to the topic guide during later interviews. Thematic analysis,[57] utilising a data-driven inductive approach,[58] will be used to identify and analyse patterns and themes of salience to participants and across the dataset using constant comparison techniques.[59 60] First, transcripts will be read several times, to gain familiarisation with the data and initial ideas. Transcripts will then be examined line-by-line with inductive codes being assigned to data segments that provide insight to participants' views and understandings. An initial coding frame will be developed and new data compared to previous data, and then to the properties of emerging categories that contain the main themes. The process of constant comparison will allow for the generation of new themes, re-classify themes and incorporate themes within other themes, with the coding frame being modified, if needed, as analysis develops. The data will be scrutinised for negative cases and reasons for the deviance explored by comparison with the whole dataset. Transcripts from the parents' and health care professionals' interviews will be analysed separately, with coding frames being developed for each separate phase. A subset of transcripts will be independently double-coded by other members of the research team and compared: any discrepancies will be discussed and resolved to achieve a coding consensus and to maximise rigour.

## 13. DATA MANAGEMENT

### 13.1. Data handling

Custodian: Head of School, Social and Community Medicine, University of Bristol.

The validated clinical database, trial management database and randomisation system will be designed so as to protect patient information in line with the Data Protection Act 1998. Trial staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centres. The participants will be identified only by a patient ID number on the CRF (both on the paper and web-based forms). All documents will be stored securely and made accessible only to trial staff and authorised personnel. The trial will comply with the Data Protection Act 1998 which requires data to be anonymised as soon as it is practical to do so.

Formal SOPs will be developed to detail each element of the data handling procedure.

A summary of the overall trial results will be made available to those parents who have confirmed that they wish to receive them. We will ask for written consent to write (after the completion of the trial, which may be three years later) to parents with a summary of the CEDAR trial results, and for parents whose child was allocated to one of the ear drop groups, further information about (i) whether they thought the child was in the active or placebo group, and (ii) the actual IMP allocation.

### 13.2. Data management

Data collection, management and archiving will be conducted in accordance with the principles of the Data Protection Act and Good Clinical Practice guidelines. We will use a secure, web-based (RedCap [Harris et al 2009]) data collection platform which will be developed, validated, hosted and supported by the University of Bristol. The system will provide a secure login to allow collaborator authentication and direct data entry, with a full audit trail. The system will also maximise access (from any primary care sites across England and Wales) while minimising risk of data loss, duplication and security lapses from laptops and other portable media. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. A bespoke web-based system will be developed to maximise the user-friendliness of data entry for clinicians and for parents.

All patients will be consented using paper consent forms, pre-numbered with the Patient ID number, and provided in the Patient Pack. Consent forms will be scanned and linked to the patient's medical record by site staff and sent by secure fax to the Bristol Centre on the day of recruitment, as well as being returned to the Bristol Centre by pre-paid return addressed envelopes.

While on-line data entry will be the default method of data capture, paper-based alternatives will be provided to accommodate clinician preference and allow recruitment to continue in the unusual event of website inaccessibility. Responsible Clinicians will be asked to enter all data onto the website by the end of day zero, except participant registration details, which will be entered by Bristol Centre staff onto an off-line trial management database. Once data are added to the web-based database, all patient paperwork (except consent forms and registration details) will be stored at the primary care site until completion of participant recruitment. Patient identifiers will be kept on a separate system from the clinical data and data protection requirements will be further enforced by best practice trial management procedures. Paper versions saved on site will be archived by the University of Bristol at the end of the trial according to local policy for paediatric clinical trials, with all data retained for at least 15 years post trial closure in line with University of Bristol procedures.

A study management system will also be developed to record the patient identifiable information and assist the study team with the workflow process. This system is developed using MS Access and SQL Server and hosted in the Bristol University data centre. It is secured using Windows network groups and secure remote access is provided using Windows Remote Desktop. The Bristol University data centre is both physically and electronically secure, with clustered servers providing resilience. All databases and network folders are backed up on a daily basis, encrypted and stored securely.

## 14. MONITORING, AUDIT, INSPECTION AND REPORTING

### 14.1. Quality assurance

The trial will be conducted in accordance with the latest approved version of the protocol, International Code on Harmonisation Good Clinical Practice (ICH GCP), relevant regulations and CEDAR Trial Standard Operating Procedures. All investigators and trial related site staff will receive training in trial procedures and ICH GCP.

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and the applicable regulatory

requirements. Data quality will be monitored and assured throughout recruitment by: (i) the Responsible Clinician accurately entering data to the web-based data collection system (e-CRF); (ii) a random 20% sample paper symptom diaries being checked against web-based data entry by the research team; (iii) recruiting sites conducting a self-audit after recruiting their first four patients; and (iv) a random 10% sample of e-CRFs will be checked by the research team. Sponsor monitoring will be undertaken in line with a risk based monitoring plan.

The independent Data Monitoring Committee (DMC), Trial Management Group (TMG) and Trial Steering Committee (TSC) will oversee the trial as described in Appendices 5 and 6.

### 14.2. Trial monitoring

***Direct access to source data / documents***
The Centre PIs and trial sites will allow monitors (from UH Bristol on behalf of the Sponsor in line with the SLA), persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data / documents. This is reflected in the Participant Information Sheet (PIS).

***Monitoring plan***
A monitoring plan will be produced by the trial team and approved by the Sponsor prior to commencement of the trial. Sponsor approval will be provided by UH Bristol in line with the SLA.

The plan will be implemented by the trial team and overseen by the R&I team at the Trust who will also act in the role of Independent Monitor, on behalf of the Sponsor, using their monitoring standard operating procedure http://www.uhbristol.nhs.uk/files/nhs-ubht/IS11-Monitoring_v3.5_15.09.2010.pdf]

***Before the trial***
The Centre PIs and trial sites will allow the monitor to visit the site and facilities where the trial will take place in order to ensure compliance with the protocol requirements. The University of Bristol's Green Light procedure will be implemented in each of the other collaborating centres (Southampton and Cardiff) in order to document preparedness to conduct recruitment locally.

***After the start of recruitment***
- The first site to recruit a child into the RCT will receive an independent monitoring visit from the R&I team at the Trust.
- All sites will be invited to complete a brief self-audit of recruitment paperwork once 2 children have been recruited to the trial. These self-audits will be checked by the trial team, and will lead to a more detailed quality check by the trial team should the rate of errors or discrepancies exceed 5%.
- 10% of participant recruitment and paper and electronic data collection will be subjected to detailed quality checks by the trial team;
- The trial team will also conduct detailed quality checks of recruitment at any site where a concern is raised by a member of the trial team or by a research participant;
- Independent monitoring visits by the R&I team will also be conducted at the request of the sponsor in the event of any serious protocol deviation which is deemed to adversely affect either the safety of one or more trial participants, or the integrity of the science behind the research.

***Independent monitoring visits (in line with monitoring policy)***
The Centre PIs will allow the monitor and/or the Sponsor to:
- Inspect the site, the facilities and the material used for the trial;
- Meet all members of his/her team involved in the trial;
- Consult all of the documents relevant to the trial;
- Check that the CRFs have been filled out correctly;
- Directly access source documents for comparison of data therein with the data in the CRFs;
- Verify that the trial is carried out in compliance with the protocol and local regulatory requirements;

- Carry out trial monitoring at regular intervals, depending on the recruitment rate, and arranged between the CI and monitor;

All information dealt with during these visits will be treated as strictly confidential.

### 14.3. Regulatory approvals and reporting

***Legislation***
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible. This research trial will be run in accordance with GCP.

The trial, including the manufacture of Investigational Medicinal Product (IMP) and placebo, will also be conducted in accordance with all applicable regulatory requirements including but not limited to:

- Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments
- EU Directive 2001/20 EC
- EU Good Manufacturing Practice (EU GMP)
- Research Governance Framework for Health and Social Care
- Declaration of Helsinki (1996)
- Medicinal Products for Paediatric Use

***Regulatory approvals***
This protocol and related documents will be submitted for review to the South Central – Oxford A Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Any subsequent protocol amendments will be submitted to the REC and MHRA, on the agreement of the Sponsor and with the prior approval of the funder, and we will make NHS organisations aware.

Annual progress reports will be submitted to the main REC. The first report will be submitted 12 months after the date on which the favourable opinion was given, and thereafter until the end of the trial. Progress reports will also be submitted to the funder in line with NIHR reporting requirements. Copies of these reports will be sent to the Sponsor prior to submission. Copies of all relevant reports will be made available to the DMC and TSC as appropriate.

***Reporting***
Development Safety Update Reports will be provided on the anniversary of the granting of CTA for the trial and sent to the MHRA and the main REC within 60 days of this date. A copy will be sent to the Sponsor prior to submission.

An end of study declaration will be submitted to the REC and MHRA within 90 days of the end of the trial. A final report at conclusion of the trial will be submitted to the NSPCR/NIHR, the Sponsor, the REC and the MHRA within one year of the end of the trial.

## 15. INTELLECTUAL PROPERTY

The foreground Intellectual Property (IP) for this project will reside with the University of Bristol. The trial ear drops will be purchased from a commercial supplier so there are no background rights required in relation to the supply and use of the drops.

## 16. ETHICAL AND SAFETY ISSUES

CEDAR will be conducted according to the principles of good research practice (including proper and appropriate conduct of research, professional integrity, honesty, statistical methods, use of data interpretation of data, non plagiarism) and the Research Governance Framework for Health and Social Care. The trial will require approval from, and comply with, NHS Ethics Committees' and Health and Safety regulations. Participation will be entirely voluntary with parents or those legally allowed to consent for children given full information regarding what trial participation involves, their right to withdraw and research dissemination plans. Parents will be given clear information about how to administer the ear drops, and about the use of the Faces Pain Scale-Revised (FPS-R [Hicks et al 2001], for children aged ≥5 years). Full written consent will be obtained from those legally allowed to consent on children's behalf, and all research staff with participant contact will have passed Disclosure and Barring Checks.

CEDAR eligibility criteria have been designed to minimise the risk of participant harm and 'Responsible Clinicians' will be reminded they retain responsibility for assessing eligibility. There are two eligibility issues to be closely monitored. First, Responsible Clinicians must be satisfied that a 'no' or 'delayed' antibiotic prescribing strategy is safe. Second, there is a theoretical risk of ototoxicity if the drops are used in the presence of a tympanic membrane perforation. Since 7% of children with AOM may experience a tympanic membrane perforation, the trial training and recruitment processes will ensure that Responsible Clinicians will be reminded to be vigilant to this potential problem, and parents will receive training to immediately recognise the signs that this has occurred (discharge from the ear), in which case further treatment with ear drops will stop. Furthermore, we will ask parents to record, in the daily Symptom and Recovery Questionnaire, whether there is any discharge from the child's ear and remind them to continue to be vigilant regarding this potential adverse event. In February 2014 we searched the MHRA and FDA web sites and neither these sites nor trials[1] of similar drops have reported this adverse event. Moreover, we will also monitor children's medical records for reports of deafness, and conduct the OMQ-14 quality of life questionnaire at 3 months, which includes questions regarding parental perception of their child's hearing.

Adverse (including serious) events will be collected directly both from parents (Symptom and Recovery Questionnaire) and at the primary care notes review. Parents will be asked to record all new symptoms (although we recognise that this may involve recording some 'normal symptoms of daily life' [Tan et al 2014] and these data will be closely monitored by the Trial Research Nurse during the follow-up telephone calls.

## 17. INSURANCE / INDEMNITY

The University has arranged insurance to compensate participants in the event of serious injury arising due, on the balance of probabilities, to their participation in the study.

## 18. FINANCE

The CEDAR trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme. Service Support Costs will be provided by the local Clinical Research Networks, and Excess Treatment Costs by the CCGs within the areas of trial recruitment.

## 19. PATIENT AND PUBLIC INVOLVEMENT

The pain of AOM consistently features as a major issue for parents and this study reflects their concern. Parents are aware that antibiotics are not analgesics and state they welcome the idea of ear drops for pain, since their experience is that children continue to experience pain even after using paracetamol, ibuprofen or both analgesic medicines.

A study specific advisory group has been recruited, involving parents with children within the age range of the study and with experience of AOM. CEDAR will also benefit from established PPI group links, including through the Bristol Health Partners Respiratory Infections Health Integration Team, a collaboration of NHS clinicians, commissioners and academics (led by Professor Hay) committed to identifying and providing the evidence needed to improve health service delivery. Existing local strategies for locating and enlisting parents will be used with coordinated systems to facilitate engagement and provide support and training to PPI participants. Parents, and their children if they choose to contribute, will be coordinated by the PPI lead (Dr Cabral) and supported to contribute to document review and teleconference discussion of pertinent issues prior to TMG and TSC meetings. Teleconferencing combined with email communication has proved very successful in enabling parents with young children to engage as all travel time is removed and access is not confined to one site. Study materials will reflect the parents input to date and subsequently.

Early consultation with parents identified a number of important points. The trial design and protocol has been informed by parents' advice, in particular: the three vs. two arm design; the acceptability of using drops for ear pain; the acceptability of using placebo drops; the importance of being able to use rescue analgesia; the use of the numerical rating pain scale for parents to record their child's ear pain; and the use of a Symptom and Recovery Questionnaire, complemented by telephone calls from the study team for monitoring children's recovery, the selection of feasible time points for outcome data collection and advice regarding the overall research burden for participating parents.

Ongoing PPI objectives will be:

1) To advise on all processes and paperwork which directly affects participants (parent or child), including the following:
   a) Use meaningful systems for recognising the impact the disease has on the child and their family e.g. the scoring systems for pain in young children that may lack the verbal capacity to explain their symptoms;
   b) Produce material such as child and parent trial information sheets in suitable language(s) and that consent forms are easily understood;
   c) Design a user-friendly paper and online Symptom and Recovery Questionnaire and follow-up system that is convenient for parents;
   d) Produce a plain English summary.

2) To contribute to decision making regarding adjustments to recruitment and retention strategies as the study unfolds; to inform the nature and content of feedback to families and lay readers regarding the outcome of the study.

Parents are also as keen to have access to the results of the research (in a format to help guide their own decision making) as they are to see the work completed for the purposes of the NHS. In addition, they are aware that literature is already offered to parents at different points of contact with health services, they have recognised the differing information needs of different groups.

## 20. DISSEMINATION

Once analyses are complete, but prior to publication, we will discuss results with as many of our stakeholders as possible, to ensure we include their perspectives of results implications. Current stakeholder list includes: parents; primary care clinicians; NICE; the MHRA; NHS England; The Royal College of General Practitioners; The Royal

College of Paediatrics and Child Health; Primary Care CCGs; Walk-in Centres; Out of Hours Centres; NHS 111; general practices; Secondary Care Trusts; and service users. In addition to final monograph for the NIHR HTA Programme, we will publish the trial results in peer-reviewed journals and present at national and international meetings.

With the assistance of our collaborators and PPI we will disseminate the study findings to a wide NHS and general audience. This will include presentations at meetings and bespoke written executive (and 'actionable') summaries for stakeholder groups such as: the MHRA; Primary Care CCGs; Walk-in Centres; Out of Hours Centres; NHS telephone services; Secondary Care Trusts; and service users.

Finally, we will send all parents a lay summary of the results, and organise fora for discussions with parents of participating children regarding the implications of the results for the management of AOM within primary care and in the home.

A CEDAR publication policy will be developed in line with University of Bristol guidance within the first 12 months of the trial, and trial publications will be subjected to an independent quality assurance procedure (as per University of Bristol protocols).

## APPENDIX 1: Ethical amendment history

| Amendment No. | Protocol Version No. | Date issued | Author(s) of change | Details of changes made |
|---|---|---|---|---|
| | 1.0 | 01 June 2015 | Harriet Downing | This is the first version of the protocol, and the version submitted for ethical approval. |
| N/A | 1.1 | 10 August 2015 | Harriet Downing | The protocol has been amended in line with the comments accompanying the provisional opinion of the Ethics Committee dated 14 July 2015, and as described in the covering letter to the Committee with the re-submission dated 10 August 2015. This version received provisional ethics approval (pending receipt by the Ethics Committee of the relevant drug documentation for the active IMP) on 26th August 2015. |
| 1 (pre ethics approval) | 1.2 | 22 January 2016 (approved by REC 03 Feb 2016) | Harriet Downing | 1. The project timetable within the trial synopsis (p10) and the trial flow diagram (p11) has been amended in line revised recruitment projections following a delay to the receipt of the trial medicines, which are expected to be ready no earlier than June 2015.<br>2. A pragmatic amendment has been made to the inclusion criteria, from (previous): "Clinician-ascertained otoscopic evidence of acute tympanic membrane inflammation (operationalised as per our previous trial[6] as: erythema with dullness or cloudiness; or bulging)" to: "Clinician diagnosis of acute otitis media (although not an entry criterion, clinicians will be asked to report the presence of otoscopic evidence of acute tympanic membrane inflammation, operationalised as per our previous trial6 as: erythema with dullness or cloudiness; or bulging)" (p6).<br>3. Clarification of an existing exclusion criterion, following the acquisition of more detailed information about Auralgan: "Known sensitivity to trial medicine" has been expanded as follows: Known sensitivity to trial medicine (Auralgan) or to its ingredients (benzocaine, phenazone, glycerine, hydroxyquinoline sulphate) or similar substances (e.g. other ester-type anaesthetics such as procaine, tetracaine)" (p6; section 6.2 on p19).<br>4. New exclusion criteria have been added, following the receipt of the SmPC equivalent information from Australia: (1) "Known porphyria or hemoglobinopathy or glucose-6-phosphate dehydrogenase deficiency or methaemaglobinaemia"; (2) "Current use of sulphonamides or antimalarials or hyaluronidase or St John's Wort". These exclusion criteria have been added due to potential complications caused by the active medicines (benzocaine and phenazone) but that have not been reported in association with the use of Auralgan. Furthermore, we anticipate that the likelihood of children |

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| | | | | presenting who meet these exclusion criteria is very small (p8; section 6.2 on p20).<br>5. Clarification has been made to the summary of the procurement of the intervention, and the manufacture of the placebo (section 7.1, p27), following the completion of the IMP supply contract.<br>6. Sections 7.2 (Packaging, labelling and dispensing, p27-28), 7.5 (Drug accountability, p29), 9.6 (Randomisation and administration of patient packs, p27) and 12.3 (Randomisation; blinding of recruiting clinicians, p48) have been revised in line with amended processes following pragmatic decisions by the Trial Management Group to (i) include the Medicine Packs within the Patient Packs, and (ii) that all Patient Packs will be dispatched directly to participating primary care sites (including those led by Cardiff or Southampton).<br>7. Section 7.3 (Storage and transport, p28) has been revised in line with our intention to store the medicines in the manner agreed with the MHRA through the CTA application process.<br>8. Additional information has been added to section 7.9 (Known side effects, p31) following the acquisition of the SmPC equivalent from the MIMS Au database, and detailed adverse events reports from the Australian Therapeutic Goods Administration.<br>9. Section 8.1 (p32): The definitions of relatedness, under the heading of 'Adverse Event Associated With the Use of the Drug' have been updated following sponsor revision of these definitions (ref http://www.uhbristol.nhs.uk/media/2518477/research_safety_reporting_sop_009_uhbristol_r_i_v8.0_19.10.15.pdf)<br>10. The SAE reporting period has been amended (section 8.2, p33) from three months, to 28 days post randomisation in line with advice from the trial sponsor. The requirement for reporting any trial-related SAE occurring after this period, to the trial sponsor, has also been clarified.<br>11. Removal of Appendix 8, 'Expected duration of the trial', due to significant delays in the start of trial recruitment as a result of IMP delays. |
| 2 | 1.3 | 25 April 2016 (approved | HD | 1) We have raised the lower age limit for participation from 6 to 12 months, at the recommendation of the Trial Steering Committee (TSC), in the light of the association of fetal haemoglobin with an increased |

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| | | by REC 13 June 2016) | | risk of benzocaine-induced methemoglobinaemia. Amendments updating the age range have been made to the eligibility criteria and throughout the whole protocol. This recommendation is in line with the TGA approved product information for Auralgan in Australia, where is it used as an over-the-counter product.<br>2) Section 7.9 (Known Side Effects) has been comprehensively revised following advice from the MHRA (received on 30 March 2016 following notice of grounds for non-acceptance and right to amend request dated 24 March 2016), to clarify:<br>i. The lack of expected side effects for Auralgan<br>ii. The conditions under which adverse events will be reported<br>iii. The rare symptoms, signs and diagnoses indicated within the Product Information as theoretical safety concerns that recruiting primary care clinicians should look out for as potential SUSARs<br>iv. The information about rare side effects that parents/carers will be made aware of<br>v. The symptoms associated with a very rare potential side effect of benzocaine topical analgesics, known as angioedema.<br>3) Section 7.4 (Dosing regimen, p28) has been clarified in line with the recommendation of the TSC that drops should be administered no more than every 2 hours and a maximum of 12 times daily, to a maximum age-specific dosage per child (whether the AOM is unilateral or bilateral), until pain is relieved, and for a maximum of 8 days. This recommendation is based on evidence of toxicity thresholds for oral administration of benzocaine.<br>4) The summary of exclusion criteria in the trial synopsis (p8), the trial eligibility criteria (section 6.2, p20) and the observational cohort study (OCS) eligibility criteria (section 6.3, p22) have been amended to clarify that:<br>the exclusion of systemically very unwell children will encompass children showing signs of respiratory distress (e.g. tachypnoea, hypoxia or recession), since respiratory distress may indicate an increased risk of potential benzocaine-induced methaemoglobinaemia;<br>vi. as well as known G6PD deficiency in the child, children will also be excluded if there is a family history of G6PD deficiency (noting that G6DP deficiency is more common in African, Asian and Mediterranean populations), on the basis |

## APPENDIX 1: Ethical amendment history

| Amendment No. | Protocol Version No. | Date issued | Author(s) of change | Details of changes made |
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| | | | | that parents are likely to know of any family history of this condition;<br>vii. the exclusion of children who need to continue taking other medicinal products containing benzocaine<br>viii. children will not be eligible for the RCT if they have previously taken part in the RCT, and children will not be eligible for the OCS if they are currently taking part or have previously taken part in the CEDAR RCT.<br>5) Section 7.8 (Concomitant Medication) has been updated to include the requirement that parents will be advised not to use any other benzocaine-containing medicinal products while using the trial ear drops.<br>6) Amendment of the study title (p1), from 'Children's drops for ear pain in acute otitis media: the CEDAR randomised controlled trial and observational cohort study' to 'Children's drops for ear pain in acute otitis media: the CEDAR randomised controlled trial'. Funder request, in order to match the title on the protocol with the title of the funded project.<br>7) The proposal for GP practices to send, at the start of each winter recruiting season, study information to the practice's registered families with children in the trial age range, has been clarified as an optional activity. Practices will be asked, but may decline, to participate in this activity. This has been clarified in the trial flow diagram (p11), Section 6.4 (Selection of participants, p22) and Section 6.6 (Addressing recruitment challenges, p25). |
| 3 | 1.4 | 01 June 2016 (approved by REC 09 August 2016) | HD | 1) Amendment of one of the CEDAR exclusion criteria applying to both the RCT and OCS, from: "*Child has proven alternative source(s) of pain other than the ear symptoms with which they are presenting*" to: "*Child has proven alternative source(s) of pain other than and more severe than the ear symptoms with which they are presenting*" in order to clarify that children with other known sources of pain, such as a sore throat, may be included if their ear pain is the over-riding source of pain (Trial Synopsis: Exclusion criteria, p8; Section 6.2, RCT eligibility criteria, p21; Section 6.3, Observational study eligibility criteria, p23)<br>2) Clarification that the exclusion criterion of otitis externa, or other disorder of the outer ear or tympanic membrane for which CEDAR ear drops should not be prescribed, applies to the AOM ear |

## APPENDIX 1: Ethical amendment history

| Amendment No. | Protocol Version No. | Date issued | Author(s) of change | Details of changes made |
|---|---|---|---|---|
| | | | | only (Trial Synopsis: Exclusion criteria, p8; Section 6.2, RCT eligibility criteria, p21; Section 6.3, Observational study eligibility criteria, p23).<br>3) Clarification that the exclusion criterion of a hearing aid which the parent feels should remain in place applies to the AOM ear only (Trial Synopsis: Exclusion criteria, p8; Section 6.2, RCT eligibility criteria, p21; Section 6.3, Observational study eligibility criteria, p23).<br>4) Due to a delay in the manufacture of the placebo, we will start the trial as a 2 arm pilot (active drops and usual care, vs usual care/no drops), for the first 3 months of the internal pilot period, to ensure that we meet the recruitment deadlines set by the funder. The third arm will be introduced as soon as the placebo is ready (Trial Synopsis: Sample size, p10; Project timetable, p10; Participant Flow Diagram, p12; Section 4.3, Justification for the trial design, p16; Section 5.2, Trial design, p17; Section 6.9, Piloting recruitment, p27)<br>5) Clarification that the decision of whether the data for children recruited to the 2 arm pilot (for the first 3 months) can be included in the final analysis will be made by the independent Trial Steering Committee based on a review of these data (Section 6.9, Piloting recruitment, p27; Section 12.1, Sampling, p51).<br>6) Clarification that a 2 arm randomisation schedule will apply during the initial 2 arm pilot, and that recruiting sites will be transferred to a 3 arm randomisation schedule for the full trial on a rolling basis (to minimise wastage of Patient Packs), once the placebo is ready (Section 7.2, Packaging, labelling and dispensing, p30; Section 9.6, Randomisation and administration of patient packs, p41; Section 12.3, Randomisation, p52)<br>7) Clarification that the UHB Pharmacy will be responsible for affixing the Medicine ID Number and the Participant ID Number to the Trial Participation Card, in line with the randomisation schedule (Section 7.2, Packaging, labelling and dispensing, p30).<br>8) Clarification that for the 2 arm pilot period, parents and clinicians will be made aware of the child's allocation to either the active treatment arm (active ear drops and usual care) or to the "control" (usual care/no ear drops arm) at the point of recruitment, following the eligibility assessment and informed consent processes (Section 7.4, Dosing regimen, p31; Section 12.3, Randomisation, p51-52) |

## APPENDIX 1: Ethical amendment history

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| | | | | 9) We wish to make provision for CEDAR eligibility assessments and IMP prescriptions to be made by appropriately trained (including GCP) non-medically qualified healthcare professionals, such as Advanced Nurse Practitioners/Prescribers (ANP), on the ground that this will pose no risk to the quality standards of the CEDAR trial which will be in line with those of standard clinical practice, and confirming the arrangements for GCP-trained GP oversight in this case (Section 6.11, Training and GCP requirements for recruiting sites, p28-29)<br>10) Section 8.3, 'Expected' adverse events and reactions, has been updated to clarify (following the safety amendments submitted within Amendment 2) that, since no known common side effects are listed in the Auralgan SmPC equivalent, any adverse event deemed related to the IMP will be regarded as unexpected.<br>11) Section 9.18 (Parental beliefs and opinions, p45) has been amended to clarify that questions relating to parental views of active vs. placebo ear drops will only be asked of parents participating in the 3 arm full trial.<br>12) The intention to update NHS organisations regarding updates to REC and MHRA approvals has been made explicit within the protocol (Section 14.3, Regulatory Approvals and Reporting, p57 (under heading 'Regulatory approvals')).<br>13) The list of investigators has been updated to reflect that Professor Margaret Fletcher has left the CEDAR study team (Trial Synopsis, Team Expertise, p11; Appendix 3, Section 1.5, Other Co-investigators, p71) |

## APPENDIX 2: Glossary of terms

| Term / acronym | Meaning |
|---|---|
| **A/B otic** | Antipyrine / benzocaine ear drops (the generic term for the CEDAR trial IMP) |
| **AE** | Adverse Event |
| **AOM** | Acute otitis media. For CEDAR, we will use a pragmatic clinical definition of AOM, similar to that used in UK primary care and previous studies , as follows: acute (≤4 days) [Singh 2006] ear pain plus otoscopic evidence of acute inflammation of the ear drum (erythema with dullness or cloudiness or bulging) as confirmed by the child's NHS clinician. |
| **Auralgan (© or ™)** | The brand name under which the CEDAR trial IMP is manufactured and marketed as a pharmacy medicine in Australia and New Zealand by Pfizer Consumer Healthcare. |
| **BRTC** | Bristol Randomised Trials Collaboration |
| **CED** | Children's Emergency Department |
| **Centre** | One of the three universities (Bristol, Cardiff and Southampton), each with a PI, from which Sites will be recruited and co-ordinated. |
| **CHU-9D** | Child Health Utility 9D quality of life questionnaire |
| **CI** | Chief Investigator |
| **CIS** | Child Information Sheet, which is given to any child who is old enough to understand what is being asked of them within the study. The CIS will have been ethically approved. |
| **Code-break** | Record held by UHBristol of allocation of active vs. placebo solution (and Medicine ID number) to Patient ID number. |
| **CRF** | Case Report Form |
| **Day 1** | The day on which the child is consented and entered into either the CEDAR RCT or the OCS |
| **Day 8** | The data collection point representing 7 days after the day of study entry |
| **DMC** | Data Monitoring Committee |
| **DSUR** | Development Safety Update Report |
| **GCP** | Good Clinical Practice |
| **Illness resolution** | The point at which the child's ear pain has been resolved for two consecutive days without the use of medication |
| **IMP** | Investigational Medicinal Product, also referred to as the "Trial Medicine". This is either active ear drops or placebo ear drops. |
| **Index consultation** | The routine consultation with the GCP-trained primary care clinician responsible for the child's routine care. |
| **Medicine ID number** | The unique number assigned to the IMP at manufacture (by the IMP manufacturer using the randomisation data provided by BRTC) and assigned, with the Patient Pack, to the Patient ID number according to the randomisation schedule provided to UH Bristol Pharmacy by the BRTC. |
| **Medicine pack** | The packaging containing the IMP uniquely identified by the Medicine ID number. |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Clinical Excellence |
| **NISCHR** | National Institute for Social Care and Health Research (Wales) |
| **OCS** | Observational Cohort Study |
| **OME** | Otitis Media with Effusion |
| **OMQ-14** | Otitis Media Questionnaire: a functional health status measure which best predicts QoL in children with otitis media |
| **OOH** | Out Of Hours clinic |
| **OTC** | Over The Counter |

## APPENDIX 2: Glossary of terms

| Term / acronym | Meaning |
|---|---|
| **Patient ID number** | The unique number already allocated to the PP which is assigned to the recruited child by the Clinician following informed written consent. |
| **Patient pack (PP)** | The pack containing all the materials necessary for recruitment. All items will be labelled with the Patient ID Number and will include the Medicine ID number (which will determine the trial arm to which the participating child is allocated), Parent and Child Information, a copy of the Symptom and Recovery Questionnaire and pen, and a thank-you voucher. |
| **PI** | Principal Investigator |
| **PIS** | The ethically approved Parent Information Sheet, which is given to the parent of the potentially eligible child on arrival at the primary care site, or by the child's Clinician, and also included in the patient pack. All parents will be provided with a PIS. |
| **QoL** | Quality of Life |
| **Randomisation data** | A list of random numbers generated by BRTC in line with the requirements of the trial sponsor and of the medicine supplier for their use in numbering the medicine packs and patient packs which are provided to UH Bristol Pharmacy. |
| **Randomisation schedule** | Instructions provided by BRTC to UH Bristol Pharmacy regarding active vs. placebo medicine allocation to Patient Packs. |
| **RCT** | Randomised Controlled Trial |
| **Responsible Clinician** | The GCP-trained primary care clinician who takes responsibility for the clinical management of the child at presentation, confirms the child's eligibility to take part in the trial, conducts the clinical examination, signs the trial prescription, consents the child / parent and explains to the parent how to administer the ear drops. |
| **SAE** | Serious Adverse Event |
| **(S)AR** | (Serious) Adverse Reaction |
| **Screening ID** | The unique number assigned to the child prior to confirming patient eligibility for recruitment into the trial during the index consultation. This number will be entered onto the trial screening log to allow for tracking of ineligible children. |
| **Site** | Recruiting primary care site, e.g. GP practice, Children's Emergency Department, Out Of Hours clinic or Walk-In Centre |
| **SLA** | Service Level Agreement |
| **SOS** | Severity of Symptoms |
| **Source data** | For the CEDAR trial, the source data will be defined as follows:<br>**Case Report Forms:** the source data will be the electronic data entered by clinicians into REDCap at the GP site within 24 hours of recruitment, either entered directly online or transcribed at the site from the paper forms.<br>**Parent Symptom and Recovery Questionnaire:** the source data for parents completing the diary online will be the electronic data they enter that is uploaded into REDCap. For parents completing paper symptom diaries, the source data will be considered to be the data recorded on the paper diary IF this is more complete than the shadow diary data collected by the trial research team in the follow-up telephone calls. For parents whose paper diaries are not returned, or where the data returned in the paper diary are less complete than the shadow data, the shadow data collected on the phone will be considered as the source data.<br>**Review of primary care medical notes:** the source data will be considered to be the electronic data entered onto REDCap at the GP practice. |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |

## APPENDIX 2: Glossary of terms

| Term / acronym | Meaning |
|---|---|
| **TGA** | Therapeutic Goods Administration. The TGA is the arm of the Australian Government Department of Health responsible for regulating therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products. Almost any product for which therapeutic claims are made must be entered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia. |
| **Trial Participation Card** | Parents of children participating in the trial will be requested to carry this with them while the child is participating in the trial. It will record the Medicine and Patient ID numbers to be used for emergency unblinding. |
| **Trial Prescription** | **The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004/1031 Schedule 1, part 2 [7]) requires that:**<br>**'The medical care given to, and medical decisions made on behalf of subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist'**<br>**The eligibility of a child to take part in the CEDAR trial must therefore be confirmed by a qualified GP.**<br><br>If the child is eligible to participate in the trial (following completion of the detailed eligibility check) the Responsible Clinician will authorise a trial prescription. This document is not intended for use by the parent or by any pharmacist and should be kept with the recruitment paperwork pertaining to the child. The purpose of the trial prescription is to confirm the issue of the trial medicine, to document the details of the medicine packs issued to the child, and to record any eligibility decisions made by the Responsible Clinician using his/her clinical judgement. The trial prescription will be completed as part of the recruitment process for children recruited to one of the two active arms of the RCT. |
| **TSC** | Trial Steering Committee |
| **VAS** | Visual Analogue Scale |
| **WIC** | (NHS) Walk-In Centre |

# APPENDIX 3: Trial management

**Trial Management**

**1.1. Sponsor**

Dr Birgit Whitman
Head of Research Governance
Research and Enterprise Development
University of Bristol
Senate House
Bristol BS8 1TH
Email: birgit.whitman@bristol.ac.uk

**1.2. Chief Investigator**

Professor Alastair Hay
GP and Professor of Primary Care
School of Social and Community Medicine
University of Bristol
Canynge Hall, 39 Whatley Road
Bristol BS8 2PS
Email: alastair.hay@bristol.ac.uk

**1.3. Trial Manager**

Harriet Downing
School of Social and Community Medicine
University of Bristol
Canynge Hall, 39 Whatley Road
Bristol BS8 2PS
Tel: 0117 331 3906
Email: harriet.downing@bristol.ac.uk

**1.4. Trial Centres**

Primary care centres based in three UK universities, led by the following Principal Investigators:

**Bristol (lead centre)**

Professor Alastair Hay
GP and Professor of Primary Care, School of Social and Community Medicine, University of Bristol
Canynge Hall, 39 Whatley Road, Bristol BS8 2PS
Tel: 0117 928 7376
Email: alastair.hay@bristol.ac.uk

**Cardiff**

Dr Nick Francis
GP and Reader, Institute of Primary Care & Public Health, Cardiff University School of Medicine
Neuadd Meirionnydd, Heath Park, Cardiff CF14 4YS
Tel: 029 20 687133, ext. 87133
Email: francisna@cf.ac.uk

**Southampton**

Professor Paul Little
GP and Professor of Primary Care Research, Primary Medical Care, University of Southampton
Aldermoor Health Centre, Aldermoor Close, Southampton, SO16 5ST
Email: p.little@soton.ac.uk

# APPENDIX 3: Trial management

### 1.5. Other Co-investigators

**Dr Ian Williamson (to September 2015)**
GP and Associate Professor, Primary Medical Care, University of Southampton

**Professor Mike Moore (from September 2015)**
Professor of Primary Care Research, Primary Medical Care, University of Southampton

**Professor Desmond Nunez**
Associate Professor and Head of Division of Otolaryngology (Head and Neck Surgery), University of British Columbia; Honorary Reader in Otolaryngology, University of Bristol

**Dr Pete Blair**
Reader in Medical Statistics, School of Social and Community Medicine, University of Bristol

**Professor William Hollingworth**
Professor of Health Economics, School of Social and Community Medicine, University of Bristol

**Dr Peter Stoddart**
Consultant in Paediatric Anaesthesia and Senior Clinical Lecturer in Anaesthesia, School of Clinical Sciences, University of Bristol

**Dr Mark Lyttle**
Consultant in Paediatric Emergency Medicine and Senior Research Fellow in Paediatric Emergency Care, Health and Applied Sciences, University of the West of England; Chair of Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI)

**Dr Jeremy Horwood**
Senior Research Fellow in Ethnography/Qualitative Social Science, School of Social and Community Medicine University of Bristol

### 1.6. Trial Statistician

**Dr Pete Blair**
Reader in Medical Statistics, School of Social and Community Medicine, University of Bristol

### 1.7. PPI (Patient / Public Involvement)
Dr Christie Cabral, Research Associate, School of Social and Community Medicine, University of Bristol

### 1.8. Trial Management and Oversight

***Trial Management Group (TMG)***
The TMG, led by the CI (Professor Hay) will comprise all Investigators, the Trial Manager, Research and Administrative staff, with input from patient / public representatives. The TMG will be responsible for trial design, conduct, management, strategy, costs, data analyses and publication. With the support of all Centre staff, the Trial Manager, will be responsible for operationalising TMG strategy and day to day trial management. The TMG will meet monthly to review detailed monitoring information regarding trial progress against the

milestones outlined in the Gantt chart. Most meetings will be by teleconference, but the TMG will also meet face to face biannually.

***Centre Management Groups***

Located in Bristol, Cardiff and Southampton, trial centre management groups will take responsibility for Centre recruitment, with Centre PIs (Hay, Francis and Little) meeting with Centre teams weekly/fortnightly as required. The Trial Manager will lead monthly Team Meeting teleconferences (taking place between the monthly TMGs), consisting of all Centre staff (trial coordinators, nurses and administrators) to operationalise TMG strategy.

***Trial Steering Committee (TSC)***

The Trial Steering Committee (TSC) will meet twice a year to provide independent supervision of the trial on behalf of the NIHR HTA. Members of the TSC are independent, i.e. have no direct involvement in the trial. In particular, the TSC will focus on trial recruitment, adherence to the protocol, patient safety and consideration of new information. We will ask an experienced, independent academic GP to chair the TSC, and independent members will include another clinical triallist, a statistician and PPI representation. Representation will be invited from the Sponsor and the NIHR HTA. The TSC will have the flexibility to meet annually or biannually depending on trial progress.

The membership will include:

- Professor Jonathan Mant, University of Cambridge **(Chair)**
- Professor Alan Smyth, Professor of Child Health & Head of Division of Child Health, Obstetrics & Gynaecology (COG), University of Nottingham
- Dr Kay Wang, GP and Academic Clinical Lecturer, Nuffield Department of Primary Care Health Sciences, University of Oxford
- CEDAR Trial CI (Professor Alastair Hay)
- One or two investigators, in line with HTA guidance
- PPI representation

Trial co-ordinators, statisticians etc will also be invited to attend as appropriate.

The TSC terms of reference can be found in Appendix 5.

***Data Monitoring Committee***

The Data Monitoring Committee (DMC) will meet twice a year, shortly before each TSC, to advise and make recommendations to the TSC regarding trial safety issues, or other reasons for the trial not to continue. If necessary, the DMC will have access to unblinded trial data. Members of the DMC are independent, i.e. have no direct involvement in the trial. The membership will include:

- Professor Toby Prevost, Professor of Medical Statistics, Dept of Primary Care and Public Health Sciences, King's College London **(Chair)**
- Professor Christian Mallen, Professor of General Practice Research, Primary Care Sciences, Keele University, Staffordshire, ST5 5 BG
- Joana Vasconcelos, Trial Statistician, Dept of Primary Care and Public Health Science, King's College London
- CEDAR Trial CI (Professor Alastair Hay)
- CEDAR Trial Statistician (Dr Pete Blair)

The DMC terms of reference can be found in Appendix 6.

***Trial Sponsor***

The trial sponsor will be the University of Bristol, and will ensure the trial meets its contractual, legal, insurance, and financial obligations, and is conducted in line with UK Clinical Trial Regulations.

# APPENDIX 3: Trial management

***Data quality***

Data quality will be monitored and assured throughout recruitment by: (i) the Responsible Clinician accurately entering data to the web-based data collection system (e-CRF); (ii) a random 20% sample paper symptom diaries being checked against web-based data entry by the research team; (iii) recruiting sites conducting a self-audit after recruiting their first four patients; and (iv) a random 10% sample of e-CRFs will be checked by the research team. Sponsor monitoring will be undertaken in line with a risk based monitoring plan.

## APPENDIX 4: Investigative Team Expertise

**Professor Hay** (CI and Bristol PI) is a GP, NIHR Research Professor and Professor of Primary Care with a track record of successfully leading and completing multicentre, primary care, randomised controlled trials and observational studies of acute infections in children and adults. Professor Hay will will take overall responsibility for leading the TMG in the design, scientific integrity, delivery, safety and publication of the trial.

**Professor Little** (Southampton PI), Professor of Primary Care Research, is a world leading infection primary care researcher. Professor Little will support the TMG in designing, delivering and publishing the trial, and as Southampton PI, will be responsible for recruitment in Southampton.

**Dr Francis** (Cardiff PI), GP and Senior Clinical Research Fellow is an established primary care paediatric infection researcher and co-lead for an HTA funded trial of children with otitis media with effusion (OSTRICH). Dr Francis will support the TMG in designing, delivering and publishing the trial, and as Cardiff PI, will be responsible for recruitment in Cardiff.

**Professor Moore** is a GP, Professor of Primary Care Research and an established primary care infection researcher. Dr Moore will support the TMG in designing, delivering and publishing the trial, and will be responsible for recruitment in Southampton.

**Dr Williamson**, GP and Senior Lecturer, is a recognised expert in primary care otitis media and hearing research. Dr Williamson will support the TMG in designing, delivering and publishing the trial, support the delivery of Southampton trial centre recruitment, and provide primary care ENT expertise.

**Professor Nunez** is an Associate Professor of Otolaryngology Head and Neck Surgery and a practicing subspecialist ear surgeon with extensive clinical and research experience in the treatment of patients with inflammatory middle ear disease and its complications. Professor Nunez will support the TMG in designing, delivering and publishing the trial and provide secondary care ENT expertise.

**Dr Blair** is a Reader in Statistics and works in the UKCRC accredited Bristol Randomised Trials Collaboration (BRTC) CTU. Dr Blair will support the TMG in designing, delivering and publishing the trial and provide statistical and methodology expertise.

**Professor Hollingworth** is a Professor of Health Economics with experience of conducting economic evaluations of acute infection in children. Professor Hollingworth will support the TMG in designing, delivering and publishing the trial and will lead the health economic evaluation.

**Dr Stoddart** is a Consultant in Paediatric Anaesthesia with expertise in pain measurement and management. Dr Stoddart will support the TMG in designing, delivering and publishing the trial and provide paediatric anaesthetics expertise.

**Dr Lyttle** is a Consultant in Paediatric Emergency Medicine, Senior Research Fellow in Paediatric Emergency Care and Chair of Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI). Dr Lyttle will support the TMG in designing, delivering and publishing the trial and will lead and advise on Emergency Department recruitment aided by his chairmanship of PERUKI, which will facilitate ED recruitment by co-ordination of research activities and mentoring new investigators in the acquisition of research skills.

**Dr Horwood** is a Qualitative Researcher, working in the UKCRC accredited Bristol Randomised Trials Collaboration (BRTC) CTU, with experience both of qualitative research into common paediatric infections and conducting qualitative evaluations of RCTs. Dr Horwood will lead the qualitative evaluation.

## APPENDIX 4: Investigative Team Expertise

**Harriet Downing** is an experienced multi-centre study manager who, as part of a multidisciplinary team, has overseen the successful recruitment and retention of over 5,000 children to the NIHR HTA funded DUTY study, and the successful recruitment of participants to the NIHR NSPCR funded OSAC trial.

We believe there are six key factors that will ensure the success of the CEDAR trial:

1. We have excellent links with the NIHR Primary Care Research Networks and strong personal relationships with regional primary care sites, who have recruited over 15,000 children to our NIHR-funded studies of acute infection in the past 5 years alone.

2. Our PPI group reports that parents are interested to try the drops, which will only be available through the trial (they are not available over-the-counter (OTC) or through the NHS), and as describe above, many parents will be aware of the trial via GP practice notification letters.

3. Given the current therapeutic limitations for ear pain in children (paracetamol and/or ibuprofen), we believe clinicians will be interested in and want to support the trial.

4. The 'light-touch' recruitment process that will fit with usual care processes and minimise disruption.

5. High rates of primary outcome ascertainment with outcomes available by the end of the first week of participation, facilitated by using tried and tested, light-touch combined paper, online and telephone data collection systems. Similar systems used in our previous studies have achieved primary outcome follow up rates in excess of 90%[6 7].

6. The use of qualitative methods to assess parent attitudes to trial participation, which will provide early warning of unanticipated challenges to the Trial Management Group (TMG).

# APPENDIX 5: Trial Steering Committee Terms of Reference

**The role of the TSC/SSC**

The role of the TSC/SSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. It should be noted that the day-to-day management of the trial is the responsibility of the Chief Investigator, and as such the Chief Investigator may wish to set up a separate Trial Management Group (TMG) to assist with this function.

The main features of the TSC/SSC are as follows:

- To provide advice, through its Chair, to the Chief Investigator(s), the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial
- To concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the trial

**Standard Constitution TSC/SSC**

The following list identifies the minimum constitution requirements, a set of outline terms of reference, and the primary reporting line for TSCs/SSCs:

- All primary research projects are required to establish a TSC (or occasionally a SSC)
- The NIHR HTA Programme Director will vet the nominees and appoint the chair and members
- All TSCs/SSCs are to have an independent chair
- All TSCs/SSCs are to have a minimum of 75% majority of independent members
- Only appointed members will be entitled to vote and the chair will have a casting vote
- The minimum quoracy for a meeting to conduct business is 67% of appointed members
- The chair and members to sign and maintain a log of potential conflicts and/or interests
- Attendance at TSC/SSC meetings by non-members is at the discretion of the chair
- The primary TSC/SSC reporting line is via the chair to the NIHR HTA Programme Director

**Composition of the TSC/SSC**

- The HTA Programme does not accept generic CTU TSCs
- An independent chair (UK based and/or holding a substantive UK based appointment)
- Independent clinicians with relevant expertise
- Independent statisticians/epidemiologists/diagnosticians with relevant expertise
- At least one individual who is able to contribute a patient and/or wider public perspective.
- Ideally, the TSC/SSC should invite observers, including a representative of the sponsor and a representative from the research network to meetings
- An indication of any proposed overseas members should have been given at the full application stage and feedback on such proposals supplied following the Commissioning Board's consideration of the application
- Although there may be periods when more frequent meetings are necessary, the TSC/SSC should meet at least annually
- Meetings should be scheduled to follow shortly after DM(E)C meetings so that reports from that group can be considered
- Minutes of meetings should be sent to all members, the sponsor, the funder and the trial master file

## APPENDIX 5: Trial Steering Committee Terms of Reference

The responsibility for calling and organising TSC/SSC meetings lies with the Chief Investigator, in association with the Chair.

There may be occasions when the Trial Sponsor or the Trial Funder will wish to organise and administer these meetings for particular trials. In the NIHR HTA programme's case this is unlikely, but it reserves the right to attend any meeting and the right to convene a meeting of the TSC/SSC in exceptional circumstances.

**The Role of the Chair of TSC/SSC**

The Chair of the TSC/SSC is directly answerable to the NIHR HTA programme, as funder. The Chair's responsibilities include:

- Arranging an inaugural meeting to finalise the protocol and to set up a schedule of meetings to align with the project plan
- Establishing clear reporting lines – to the Funder, Sponsor, etc.
- Being familiar with relevant guidance documents and with the role of the DM(E)C
- Providing an independent, experienced opinion if conflicts arise between the needs of the research team, the funder, the sponsor, the participating organisations and/or any other agencies
- Leading the TSC/SSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems
- Ensuring that changes to the protocol are debated and endorsed by the TSC/SSC; letters of endorsement should be made available to the project team when requesting approval from the funder and sponsor for matters such as changes to protocol
- Being available to provide independent advice as required, not just when TSC/SSC meetings are scheduled
- Commenting on any extension requests and, where appropriate, providing a letter of recommendation to accompany such a request
- Commenting in detail (when appropriate) regarding the continuation or termination of the project

I**ndependence**

The definition of independent is as follows:

- Not part of the same institution as any of the applicants or members of the project team
- Not part of the same institution that is acting as a recruitment or investigative centre
- Not related to any of the applicants or members of the project team
- For the chair only – not an applicant on a rival proposal.

# APPENDIX 6: Data Monitoring Committee Terms of Reference

**The role of the DM(E)C**

The DMECs main role is as follows:

- It is the only body involved in a trial that has access to the unblinded comparative data
- The role of its members is to monitor these data and make recommendations to the TSC/SSC on whether there are any ethical or safety reasons why the trial should not continue
- The safety, rights and well-being of the trial participants are paramount
- The DM(E)C considers the need for any interim analysis advising the TSC/SSC regarding the release of data and/or information
- The DM(E)C may be asked by the TSC/SSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies
- If funding is required above the level originally requested, the DM(E)C may be asked by the Chief Investigator, TSC/SSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial
- Membership of the DM(E)C should be completely independent, small (3- 4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statistician
- Responsibility for calling and organising DM(E)C meetings lies with the Chief Investigator, in association with the Chair of the DM(E)C. The project team should provide the DM(E)C with a comprehensive report, the content of which should be agreed in advance by the Chair of the DM(E)C
- The DM(E)C should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be fed into the TSC/SSC
- Minutes of meeting should be sent to all members, the sponsor, the funder, the TSC and the trial master file. It should be noted that the minutes may have 'in camera' items redacted from some copies

**Standard Constitution DM(E)C**

The following list identifies the minimum constitution requirements, a set of outline terms of reference and the primary reporting line for DM(E)C:

- Most primary research projects are required to establish a DM(E)C
- The NIHR HTA Programme Director will vet the nominees and appoint the chair and members
- All DM(E)C members are to be independent (with at least one member being UK based and/or holding a substantive UK based appointment)
- Only appointed members will be entitled to vote and the chair will have a casting vote
- The minimum quoracy for a meeting to conduct business is 67% of appointed members
- The chair and members to sign and maintain a log of potential conflicts and/or interests
- Attendance at DM(E)C meetings by non-members is at the discretion of the chair
- The primary DM(E)C reporting line is via the chair to the TSC/SSC

**Independence**

The definition of independent is as follows:

- Not part of the same institution as any of the applicants or members of the project team
- Not part of the same institution that is acting as a recruitment or investigative centre
- Not related to any of the applicants or members of the project team
- For the chair only- not an applicant on a rival proposal

## APPENDIX 7: Study outcome definition and measurement

| Research question | Question and outcome type | Outcome measure | Presented as | Method of outcome data collection |
|---|---|---|---|---|
| 1.1 Do active drops lead to a lower proportion of children consuming antibiotics by Day 8 (where Day 1 is the day of randomisation) compared with no drops (usual care)? | Primary | Binary (yes/no): 'any antibiotics' consumed by Day 8 vs 'none' | The proportion of children recruited who have been given any antibiotics by mouth within the first 7 days post randomisation | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1; GP records |
| 2.1 Do active drops provide superior pain relief in the first 24-36 hours compared to placebo drops? | Key secondary | Ordinal: Parent-rated child's ear pain score at 24-36 hours, using the zero to ten rating scale | Mean/Median/Log mean ear pain score (0-10) over the 24-36 hours since randomisation (depending on the distribution). | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1 |
| 2.2 Do active drops lead to reduced oral analgesic consumption in the first 7 days after randomisation compared with placebo drops? | Secondary | Numeric: Analgesic use at Day 8 = number of doses of paracetamol and/or ibuprofen and/or other pain-relieving agents | Mean/Median/Log mean number of doses in the first 7 days after randomisation (depending on the distribution). | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1 |
| 2.3 Do placebo drops provide superior pain relief in the first 24-36 hours compared to 'no drops' (usual care)? | Secondary | Ordinal: Parent-rated child's ear pain score at 24-36 hours, using the zero to ten rating scale | Mean/Median/Log mean ear pain score (0-10) over the 24-36 hours since randomisation (depending on the distribution). | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1 |
| 2.4 Do active drops lead to a lower proportion of children consuming antibiotics by Day 8 (where Day 1 is the day of randomisation) compared with placebo drops? | Secondary | Binary: 'any antibiotics' consumed by Day 8 vs 'none' | The proportion of children recruited who have taken any antibiotics by mouth within the first 7 days post randomisation | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1 |
| 2.5 Do active drops alter the number of days before starting antibiotics in the first seven days post randomisation, compared with placebo drops and no drops (usual care)? | Secondary | Numeric: number of days post randomisation to first consuming antibiotics | For children who have started taking antibiotics, the average number of days after recruitment for which antibiotics were not given (delayed) | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1 |

## APPENDIX 7: Study outcome definition and measurement

| Research question | Question and outcome type | Outcome measure | Presented as | Method of outcome data collection |
|---|---|---|---|---|
| 2.6 Do active drops reduce overall symptom burden (including episodes of crying/ distress, disturbed sleep, interference with normal activity, appetite and fever) in the first 7 days after randomisation compared to placebo drops and no drops (usual care)? | Secondary | Numeric: Total number of symptoms and average severity of symptoms over the first 7 days after randomisation | Mean/Median/Log mean severity of other symptoms in the first 7 days after randomisation (depending on the distribution). | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1 |
| 2.7 Do active drops alter overall illness duration (defined as the last day post randomisation on which parent-reported child ear pain scores zero for two consecutive days without other analgesic medication) compared to placebo drops and no drops (usual care)? | Secondary | Numeric: number of days post randomisation on which the parent reports a score >0 for the child's ear pain or gives the child analgesics for ear pain | Number of days until child's ear pain resolves for two consective days pain free without medication (this will give us a start date but not necessarily an end date for antibiotic consumption). | Daily Symptom and Recovery Questionnaire (Days 1-8) with telephone support calls during week 1 |
| 2.8 What are the net incremental costs to the NHS (e.g. fewer antibiotic prescriptions) and society (e.g. parental productivity) of using active ear drops compared to no drops (usual care) in the short (7 days after randomisation) and medium term (3 months)? | Secondary | To be defined in the Economic Analysis Plan | To be defined in the Economic Analysis Plan | Symptom and Recovery Questionnaire (Day 8) with telephone support call, and review of primary care medical notes at 3 months |
| 2.9 To conduct an economic analysis to explore whether the net incremental costs of active ear drops are justified by improved pain relief, symptom burden, antibiotic use or quality of life. | Secondary | To be defined in the Economic Analysis Plan | To be defined in the Economic Analysis Plan | Symptom and Recovery Questionnaire (Day 8) with telephone support call, review of primary care medical notes at 3 months, and QoL postal questionnaire at 3 months |
| 2.10 To use qualitative methods to investigate parents' and clinicians' views | Secondary | | | Qualitative interviews |

## APPENDIX 7: Study outcome definition and measurement

| Research question | Question and outcome type | Outcome measure | Presented as | Method of outcome data collection |
|---|---|---|---|---|
| and experiences of AOM in children in the CEDAR trial, and specifically to: | | | | |
| 2.10.1 To explore through qualitative methods parents' views, beliefs and expectations about AOM and its treatment. | Secondary | N/A | Inductive thematic analysis using constant comparison techniques. | Qualitative interviews with parents |
| 2.10.2 To understand parents' and clinicians' experiences of the trial, including their experiences and opinions of treatments for AOM, including barriers, facilitators and adherence to treatments. | Secondary | N/A | Inductive thematic analysis using constant comparison techniques. | Qualitative interviews with parents and clinicians |
| 2.10.3 To examine reasons for parents' declining trial participation or withdrawing from the trial | Secondary | N/A | Inductive thematic analysis using constant comparison techniques. | Qualitative interviews with parents who decline trial participation |
| 2.10.4 In preparation for disseminating the trial results, to explore the information and support needs of parents and clinicians in relation to AOM and its treatment. | Secondary | N/A | Inductive thematic analysis using constant comparison techniques. | Qualitative interviews with parents and clinicians |
| 2.11 To investigate the representativeness of the CEDAR trial sample by describing the presentation, management and outcome of children with AOM in primary care. | Secondary | To be defined after data collection and analysis | To be defined after data collection and analysis | Database Search, Screening Log and Case Report Form (for RCT and observational cohort study) |

## APPENDIX 8: Auralgan Product Information (PI-Auralgan_2015-05-07A)

# Auralgan Ear Drops

**PRODUCT INFORMATION**

**Product description**

Auralgan Ear Drops is a clear colourless to light amber viscous liquid.
Refer to presentation for a complete description of the dosage form.
Each 1mL of ear drops solution contains:

Phenazone, 54mg
Benzocaine 14mg

This product also contains hydroxyquinoline sulfate and glycerol.

**Pharmacology**

**Pharmacokinetics:**

Phenazone is absorbed from the gastro-intestinal tract and distributed throughout the body fluids. Less than 10% is bound to plasma proteins and it has a half-life of about 12 hours. Phenazone is metabolised in the liver to 3 major metabolites 3-hydroxymethyl-phenazone, 4-hydroxyphenazone, and norphenazone. Phenazone, 3-hydroxymethylphenazone, and glucuronidated metabolites are all excreted in the urine. A small proportion may be eliminated via the bile.

Benzocaine, like most local anaesthetics, is readily absorbed through mucous membranes, and through damaged skin. Local anaesthetics are weak bases and at tissue pH can diffuse through connective tissue and cellular membranes to reach the nerve fibre where ionisation can occur.
Anesthetics of the ester-type are hydolzed by esterases in the plasma and to a lesser extent in the liver. Most ester-type anesthetics have little protein binding.

**Pharmacodynamics/Mechanism of action:**

Phenazone is a non-steroidal anti-inflammatory drug (NSAID). The mechanism of action for otic use has not been established.

Benzocaine is an ester type local anesthetic. It is an ethyl ester of paraaminobenzoic acid (PABA) and has been used widely as a topical anesthetic. It shares the pharmacologic effects of other local anesthetics, and acts by blocking nerve conduction first in the autonomic, then in sensory and finally motor nerve fibers. Nerve conduction appears to be blocked by benzocaine as a result of a decrease in the permeability of the nerve cell membrane to sodium ions. Competition with calcium ions for membrane binding sites also appears to be involved. Local anesthetics may also reduce the permeability of resting nerves to potassium, as well as to sodium ions.

## APPENDIX 8: Auralgan Product Information (PI-Auralgan_2015-05-07A)

Due to its low aqueous solubility, benzocaine is poorly absorbed and systemic toxicity is rare however, methemoglobinemia has been observed following topical application.

**Indications**

Auralgan ear Drops is for the effective relief of ear pain associated with otitis media.

**Contraindications**

Auralgan Ear Drops is contraindicated for use:

- in patients with perforated ear drums
- if discharge from the ear is present
- in patients with known hypersensitivity to any of the ingredients in the product or to similar substances

**Precautions**

Auralgan Ear Drops should be used with caution in patients with the following ear problems:

- Pain lasting more than 24 hours
- Fever, dizziness, stiff neck, ear discharge
- Hearing loss or ringing in the ears
- Inability to walk properly
- In patients who have had a discharge from ears, a recent ear infection or had a burst ear drum in the past.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been performed to evaluate the carcinogenic or mutagenic potential of Auralgan Ear Drops. The effect of Auralgan Ear Drops on human fertility is not known.

Auralgan Ear Drops should be used with caution in patients with porphyria as phenazone is possible porphyrogenic.

This product should be kept out of reach of children.

Due to a potential increased risk of methemoglobinemia, use with caution in the following patients:

- Patients taking drugs such as sulphonamides or antimalarials as these may predispose to methemoglobinemia.
- Infants under 1 year of age.
- Patients with hemoglobinopathies or Glucose-6-phosphate dehydrogenase deficiency (G6PD).

Stop use and seek immediate medical attention if you have difficulty breathing; pale, gray or blue colored skin; weakness, confusion, or headache. These may be signs of a rare, but serious condition and may appear within minutes to hours after benzocaine use.

# APPENDIX 8: Auralgan Product Information (PI-Auralgan_2015-05-07A)

*Use in pregnancy*

The safe use of Auralgan Ear Drops during pregnancy has not been established.

*Lactation*

Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Therefore it is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.

*Interaction with other medicines*

- Hyaluronidase - effectively increases the diffusion of local anesthetics. The beneficial effects of hyaluronidase are offset by an increased incidence of systemic toxic reactions due to increased absorption of the local anesthetic
- St John's Wort – may increase the risk of cardiovascular collapse and/or delayed emergence from anesthesia

**Adverse reactions**

Due to its low aqueous solubility, benzocaine is poorly absorbed and systemic toxicity is rare however, methemoglobinemia has been observed following topical application.

Benzocaine may cause the following symptoms: nausea and vomiting, whereas, Phenazone has been associated with the haemolytic anemia and agranulocytosis. Such reactions are unlikely following application of Auralgan on the external ear canal.

Hypersensitivity reaction consisting of rash, urticaria, oedema, anaphylaxis have been observed rarely with Benzocaine.

Symptoms such as vertigo, nausea, and nystagmus has been observed after local anaesthetic use in the external or middle ear and may be due to penetration of the local anaesthetic into the inner ear.

Individuals frequently exposed to ester-type local anaesthetics can develop contact dermatitis characterised by erythema and pruritis which may progress to vesiculation and oozing. Discontinue promptly if sensitisation or irritation occurs.

**Dosage and Administration**

- Use Auralgan Ear Drops at room temperature.
- If bottle is cold to the touch, warm in hand for a minute.
- Tilt head to one side with affected ear uppermost.
- Fill ear canal and plug ear with cotton wool moistened with Auralgan Ear Drops.
- Repeat every 1 to 2 hours until pain is relieved.

## APPENDIX 8: Auralgan Product Information (PI-Auralgan_2015-05-07A)

- If conditions persist, a doctor should be consulted.
- Avoid touching the ear with the dropper.
- Do not rinse dropper after use.
- Replace dropper in the bottle after use and cap tightly.

**Overdosage**

In case of accidental ingestion, contact the Poison Information Centre (Australia 13 11 26; New Zealand 0800 764 766) immediately.

**Presentation**

Auralgan Ear Drops is a clear colourless to light amber viscous liquid, packed in bottle.

Marketed pack size: 15mL

**Storage**

Store below 25°C

**Poison Schedule**

Auralgan Ear Drops: Pharmacy Medicine

**Name and address of the Sponsor:**

Pfizer Australia Pty Limited
38-42 Wharf Road
West Ryde NSW 2114 Australia
Australia ☎ Toll Free 1800 555 057

Pfizer New Zealand Ltd
Auckland, New Zealand
New Zealand ☎ Toll Free 0800 447 400

**Date of TGA Approval : 16 April 2014**

**Date of Last Amendment: 3 July 2015**

## APPENDIX 9: Randomisation, concealment and code-break

Each child for whom formal consent has been given by the parent or legal guardian will be randomised to one of the three arms of the trial: active ear drops plus usual care, placebo ear drops plus usual care, and usual care alone.

The randomisation schedule will be written by BRTC and will be stratified by Centre (Bristol, Cardiff, Southampton), with trial medicines (identified by a Medicine ID number) centrally randomised to patient packs (identified by a Participant ID number). The Centres will be provided with identical, sealed, sequentially numbered Patient Packs and with identical, sealed, numbered Medicine Packs (each containing a bottle of the active or placebo ear drops) to distribute to participating primary care sites. The centres will receive Patient Packs and Medicine Packs in a proportion of 3:2, in line with the ratio of treatment arms (usual care plus active drops or placebo drops) to the control arm (usual care and no drops). The sites will also receive Patient Packs and Medicine Packs in a proportion of 3:2.

Recruiting primary care sites will be given a set number of identical, sealed Patient Packs which will be distinguished by the unique Participant ID numbers. They will also be provided with a set of Medicine Packs which will be identified by the unique Medicine ID numbers. The patient packs will each contain a pre-randomised Medicine ID number. The format of the Medicine ID number will specify whether the participant will be allocated to a treatment group (either the active ear drops or placebo ear drops, but the specific group will be concealed) or to the control arm. For participants in the treatment arms the Medicine ID number in the Patient Pack will match the Medicine ID number on one of the Medicine Packs with which the site has been provided. For participants in the control arm, there will be no Medicine Pack with a matching Medicine ID number.

Once participant eligibility is confirmed and written informed consent obtained, the parent will be given the next available sequentially numbered Patient Pack. If the Medicine ID number indicates that the child has been allocated to one of the medicine arms, the clinician will retrieve the single bottle of ear drops for which the Medicine ID number corresponds to that provided in the Patient Pack. For participants in the treatment arms, Quality Assurance will be achieved by asking a third party (another member of the practice team) to verify that the Medicine ID number in the Patient Pack has been correctly matched to the Medicine ID number on the Medicine Pack containing the bottle. For participants in the control arm, no matching will be necessary.

The patient ID number will be different to the Medicine ID number to enable flexibility in the numbers recruited at each Centre, allowing medicine packs to be combined with patient packs allowing for temporary fluctuations in recruitment rates between Centres.

The primary research question ("do drops reduce antibiotic consumption") is best addressed using a pragmatic, open design since knowledge of treatment allocation (as well as the treatment itself) is known to be an important driver of antibiotic consumption [Little BMJ 2001] and will provide estimates of 'real world' pragmatic effect sizes. However, to investigate effects on pain (subjective outcome and secondary research question) requires a blinded design. One of the reasons to have a 1:1:1 randomisation strategy in the three arms is that the trial statistician will be blind to patient allocation.

The UH Bristol Pharmacy will hold the randomisation schedule and a log of which Medicine Pack was put into which Patient Pack (hereafter referred to as the Code-break) and provide a 24 hour emergency unblinding service. During working hours (Monday to Friday, 9am to 5pm), concerned clinicians should contact the UH Bristol Pharmacy Clinical Trials Unit on 0117 342 4175. Out-of-hours, the Trust on-call Emergency Duty Pharmacist is available via the Trust switchboard 0117 923 0000. Each parent will be given a Trial Participation Card with details of who the child's Responsible Clinician should contact in the event of an emergency. The Trial Manager and Centre Co-ordinators will also hold these cards.

A standardised procedure for breaking the code will be available (UH Bristol CT 5 01 Emergency Code Breaking). When necessary, the code for a particular participant can be broken at any moment during the trial. The codes will only be broken in case of a medical emergency, if unblinding will influence the child's treatment, or the child

## APPENDIX 9: Randomisation, concealment and code-break

has suffered an unexpected serious adverse event (e.g. anaphylaxis; admission to hospital with life threatening illness (e.g. septicaemia; meningitis; severe pneumonia requiring ITU admission; death)).

The Code-break will only be released to the investigative team once written confirmation has been received that primary outcome data analysis is complete. The UH Bristol Pharmacy will also record a list of all participants and their treatment allocation and file this in the pharmacy trial file and provide a copy to the Trial Manager at the end of the trial. Formal SOPs will be developed to describe each of these procedures in detail.

## APPENDIX 10: Participant Withdrawal

Parents have the right to withdraw their children, and children have a right to withdraw themselves, from the trial at any time for any reason, without their medical care being affected. Parents and children also have the right to decline to continue with any aspect of the research, without withdrawing and without their medical care being affected.

Data already collected will continue to be used in the trial and parents who withdraw their children from the trial will be asked if they are still willing to provide follow-up data via the Symptom and Recovery Questionnaire. Furthermore, we intend to conduct telephone interviews with parents who decide to withdraw (n=10). If a child is withdrawn, the reason for and type of withdrawal will be documented in the CRF. For example, type of withdrawal may include:

1. Trial use of baseline (CRF) data
2. Use of trial medication
3. Completing Symptom and Recovery Questionnaire
4. Receiving telephone calls, letters, email or texts to support Symptom and Recovery Questionnaire completion
5. Review of their primary care record
6. Completion of the postal Quality of Life (QoL) questionnaire at 3 months
7. Any combination or all of the above

The Principal Investigators also have the right to withdraw children from the trial drug in the event of inter-current illness, Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), protocol violations, administrative reasons or other reasons. The reason for withdrawal will be documented in the CRF. If the child is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. It is understood by all concerned that an excessive rate of withdrawals can render the trial un-interpretable, therefore unnecessary withdrawal of children will be avoided.

We will request return of the trial Medicine Packs from the parents of children who are withdrawn from the trial. Recruitment will continue until the required number of follow-up datasets are received, thereby replacing any children who have been withdrawn before Symptom and Recovery Questionnaire outcomes are collected.

A formal SOP will be developed to describe the process for declining to continue with elements of the research and for withdrawing from the trial.

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***The following citations are to be linked to references to the CHU-9D:***

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