IMMEDIATE ORAL, IMMEDIATE TOPICAL OR DELAYED ORAL ANTIBIOTICS FOR ACUTE OTITIS MEDIA WITH DISCHARGE:

The Runny Ear STudy

(REST)

the runny ear study

V5.0

10th May 2018

This protocol has regard for the HRA guidance

FULL / LONG TITLE OF THE TRIAL

Immediate Oral, Immediate Topical or Delayed Oral Antibiotics for Acute Otitis Media with Discharge: The Runny Ear Study

SHORT TRIAL TITLE / ACRONYM

REST

PROTOCOL VERSION NUMBER AND DATE

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1. (Pre-MHRA approval)	V4.0	17th April 2018	Kathryn Curtis	Additional exclusion criteria added and SAE reporting updated for clarity
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RESEARCH REFERENCE NUMBERS

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i. LIST OF ABBREVIATIONS

AE	Adverse Event
AOM	Acute otitis media
AOMd	Acute otitis media with discharge
API	Application Programming Interface
BNFfC	British National Formulary for Children
BRTC	Bristol Randomised Trials Collaboration
AR	Adverse Reaction
CA	Competent Authority
CAPC	University of Bristol Centre for Academic Primary Care
CDISC	Clinical Data Interchange Standards Consortium
CDIIM	Clinical Data Information Integration Model
CI	co-Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DNC	Data Node Connector
DBS	Disclosure and Barring Service
DH	Department of Health
DIBD	Developmental International Birth Date
DM(E)C	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EHR	Electronic Health Record
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
EU GMP	European Union Good manufacturing Practice
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IMP	Investigational Medicinal Product
ICL	Imperial College London
IP	Intellectual property
ISRCTN	International Standard Randomised Controlled Trials Number
KCL	Kings College London
MA	Marketing Authorisation
MALDI-TOF	Matrix-assisted Laser Desorption/Ionization Time-of-Flight

MHRA	Medicines and Healthcare products Regulatory Agency
MIC	minimum inhibitory concentration
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NHS FP10	NHS prescription
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHR CRN	National Institute for Health Research Clinical Research Network
MRC	Medical Research Council
OM6	Otitis Media-6 questionnaire
ODM	Operational Data Model
OTC	Over the Counter medicines
PPI	Patient and Public Involvement
PI	Principal Investigator
PIS	Participant Information Sheet
PROMs	Patient Reported Outcome Measure
RCT	Randomised Control Trial
RCPCH	The Royal College of Paediatrics and Child Health
RCGP	The Royal College of General Practitioners
REC	Research Ethics Committee
R&I	Research and Innovation
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SFTP	Secure File Transfer
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SRQ	Symptom Recovery Questionnaire
SDM	Study Data Model
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TRANSFoRm	Electronic data collection tool
TSC	Trial Steering Committee
UHBristol	University Hospital Bristol NHS Foundation Trust
US FDA	US Food and Drug Administration

ii. TRIAL SUMMARY

Trial Title	Immediate oral, immediate topical or delayed oral antibiotics for acute otitis media with discharge: The Runny Ear Study	
Internal ref. no. (or short title)	REST	
Clinical Phase	Phase IV	
Trial Design	Three-arm randomised trial	
Trial Participants	Children aged ≥12 months to <16 years with acute otitis media (AOM) with discharge (AOMd)	
Planned Sample Size	399	
Treatment duration	7 days	
Follow up duration	3 months	
Planned Trial Period	26 months: July 2018-October 2020 including pilot and follow up	
	Objectives	Outcome Measures
Primary	To determine whether either ciprofloxacin 0.3% drops or delayed oral amoxicillin (clarithromycin if penicillin allergic) are non-inferior to current usual care (immediate oral antibiotics) for overall illness duration in children with AOMd presenting to primary care.	Time to resolution of: • Pain • Fever • Being unwell • Sleep disturbance • Otorrhoea • Episodes of distress/crying being rated 'no' or 'very slight' problem (without need for analgesia) Recorded by parents/legal guardians using a validated[1 2] Symptom and Recovery Questionnaire (SRQ) with Research Nurse telephone support.

Secondary	1. To estimate the short-term cost-implications of immediate topical or delayed oral antibiotics compared with immediate oral antibiotics from the perspective of the National Health Service (NHS) 2. To compare effects on duration of 'moderately bad or worse' symptoms; parent/legal guardian satisfaction with treatment; and adverse events 3. To compare hearing loss and AOM/AOMd recurrence rates at 3 months 4. To understand parent/ legal guardian and clinician views of AOMd trial participation, adherence and satisfaction with allocated treatment. 5. To evaluate the impact of treatment on carriage of antibiotic resistance in the gut	• Duration of 'moderately bad or worse' symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea) • Episodes of distress/crying • Appetite and interference with normal activities, SRQ up to 14 days • Antibiotic and analgesic use (SRQ) • Adverse events (diarrhoea, rash, vomiting, serious complications, SRQ) • Treatment adherence and cross over (SRQ) • Parent/ legal guardian satisfaction with treatment (SRQ) • NHS resource use and costs at 14 days (SRQ) • Repeat AOM and AOMd episodes, serious complications and OM6 hearing questionnaire at 3 months • Secondary care resource use and costs at 3 months • Qualitative evaluation of recruitment, medication satisfaction, adherence and follow up. • Analysis of stool sample to assess burden of resistance

Investigational Medicinal Products	Ciprofloxacin 0.3% drops Amoxicillin (or another suitable antibiotic as prescribed by the GP) Clarithromycin (if penicillin allergic) (or another suitable antibiotic as prescribed by the GP)
Formulation, Dose, Route of Administration	Ciprofloxacin: four drops three times daily for seven days Amoxicillin: dosed by age, three times daily for seven days Clarithromycin: does by weight/age, twice daily for seven days

iii. FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON-FINANCIALSUPPORT GIVEN**
National Institute for Health Research Health Technology Assessment	Grant funding
National Institute for Health Research Clinical Research Networks	Service Support Costs
Participating CCGs	Excess treatment costs

iv. TRIAL MANAGEMENT

Sponsor and Host

NHS Bristol CCG will be the host organisation for this research. The CCG will oversee the implementation of all aspects of the study and will ensure the trial meets its contractual, legal and financial obligations. The Sponsor will be the University of Bristol who will ensure the Trial has adequate insurance and meets all regulatory obligations. The Trial will be run in accordance with Bristol Randomised Trials Collaboration (BRTC) Standard Operating Procedures (SOP): SOP-IT-004 Data Management, SOP-QM-001 Quality Management, SOP-TM-001 Trial Start Up, SOP-TM-002 Trial Conduct, SOP-TM-003 Trial Closure. In addition, the co-Investigators (CI) and Trial Manager will be trained on these SOPs to ensure adherence.

Funder

This research is funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (funder ref: 16/85/01).

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health (DH).

Trial Steering Committee (TSC)

The Trial Steering Committee will meet twice a year to provide independent supervision of the trial on behalf of the National institute for Health Research Health Technology Assessment (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:

- Chair: Professor Jonathan Mant, University of Cambridge
- Independent member: Dr Fiona Warren, University of Exeter
- Independent member: TBC
- REST Trial co-CI (Professor Alastair Hay and Professor Mike Moore)
- PPI member: Catherine Hamilton

Data Monitoring and Ethics Committee (DM(E)C)

The Data Monitoring and Ethics Committee 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:

- Chair and statistician: Professor Toby Prevost, Imperial College London
- Independent member and clinician: Professor Christian Mallen, Keele University
- Independent member and clinician: Dr Fiona Hamilton, University College London
- REST Trial Co-CI (Professor Alastair Hay and Professor Michael Moore)
- REST Trial Statistician (Professor Richard Morris) or the BRTC Statistics Research Associate where appropriate i.e.in the instance of unblinded interim analysis for the DMC to maintain the blinded status of the Senior Trial Statistician.

Co-Chief Investigators

Professor Hay and Professor Moore will take overall responsibility for leading the TMG in the design, scientific integrity, delivery, safety and publication of the trial, on time and within budget.

Trial Management Group

All applicants will be TMG members and will support design, delivery and publication.

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 on a regular basis to review detailed monitoring information regarding trial progress against the milestones outlined in the Gantt chart, see appendix 1.

TRANSFoRm

Professor Delaney will be responsible for TRANSFoRm functionality in REST. Dr Vasa Curcin will lead the KCL team, managing the TRANSFoRm platform. Professor Delaney and the KCL TRANSFoRm team will have regular workflow and technical meetings with the Bristol research group.

PPI

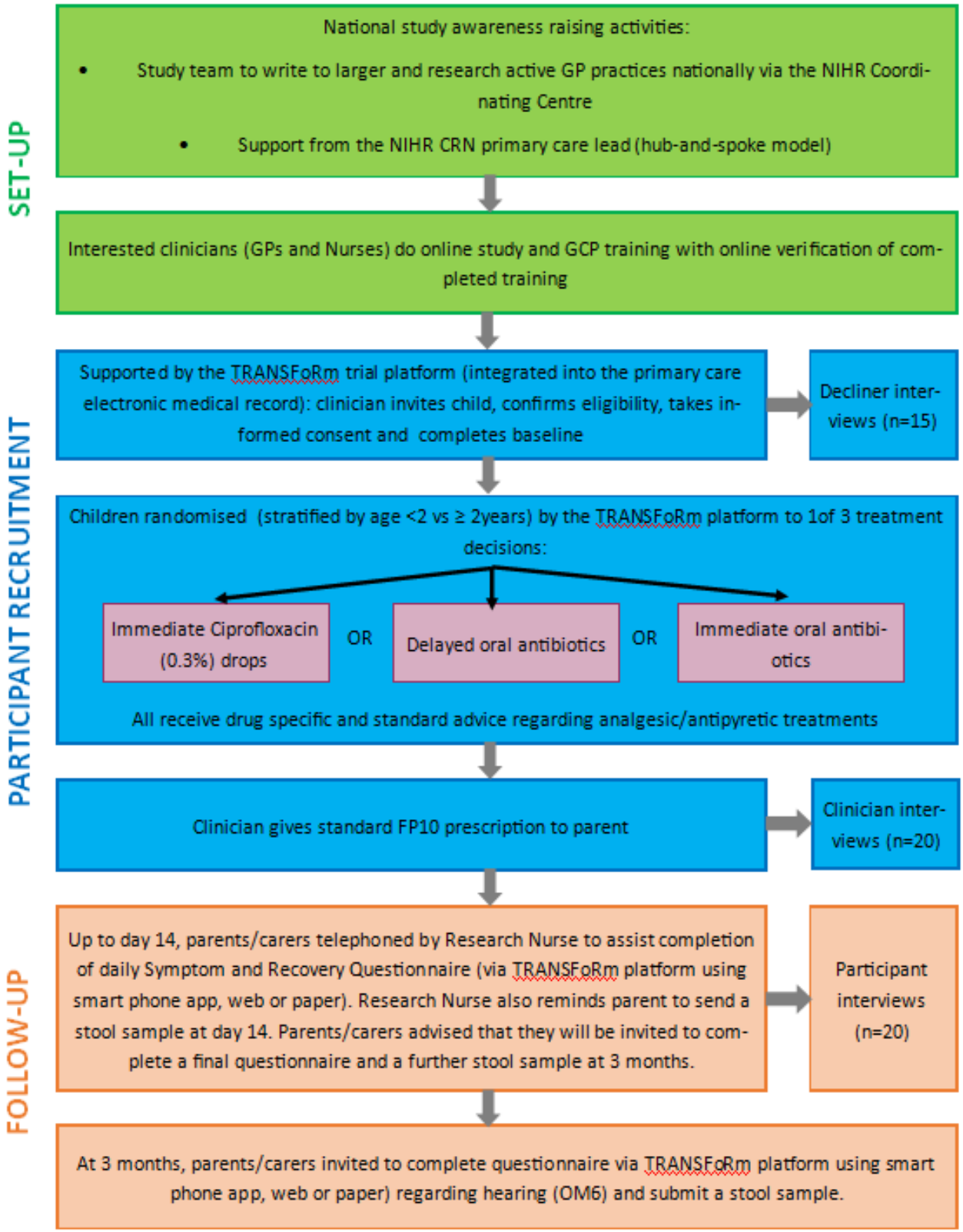
PPI contributors will fulfil a number of roles:

- in conjunction with the PPI coordinator and CAPC communications officer, create parent/ legal guardian and patient-facing materials, write print media releases, utilise social media ensuring that these materials and approaches are parent/ legal guardian/child friendly with minimal burden;
- during recruitment, PPI meetings will focus on: troubleshooting and advising on site and parent/ legal guardian newsletters to inform the TMG;
- at the end of the study, PPI meetings will focus on: interpreting results and dissemination methods. PPI members will help identify non-academic dissemination avenues, and will advise on materials for press releases, print media, social media and parent/ legal guardian facing materials, including presentation of results using a parent/ legal guardian/child friendly animation.

CTU

The CTU, Bristol Randomised Trials Collaboration, will oversee the management of the trial on a day-to-day basis, attend the TMG and provide methodological support throughout. BRTC will conduct the statistical, economic and qualitative analysis.

v. TRIAL FLOW CHART



1. PLAIN ENGLISH SUMMARY

Middle ear infections (medical term: 'acute otitis media' or 'AOM') are common painful infections in children. There were 2.8M treatment episodes for AOM in 2011 in England and Wales. Germs multiply in the confined middle ear resulting in a build-up of pressure that stretches the eardrum. In around 1 in 7 children, the eardrum bursts, releasing a liquid (medical term: 'discharge' or 'otorrhoea') that can be seen coming out of the ear. It is commonly believed, that the pain of AOM improves when the eardrum bursts, but our research shows the pain is similar, with or without the eardrum bursting.

At the moment, nearly all UK children with AOM and discharge (AOMd) seen by their GP/nurse are treated with antibiotics by mouth. These can cause side-effects like rashes, diarrhoea and vomiting and more rarely, severe allergic reactions. They can also make the germs in a child's body resistant to antibiotics.

It may be possible to use alternative treatments for ear discharge. One possibility is to use antibiotic eardrops; our research has shown these are better than antibiotics by mouth for children with runny ears and grommets, probably because the antibiotics are given directly to the place they are most needed. Another potential treatment is a 'delayed' antibiotic prescription (where parents are advised to wait to see if the child's infection improves without antibiotics). Our studies in other infections suggest this can be just as effective and safe, but with fewer side effects.

Since AOMd is painful and distressing for children and their families it is important to show that any new treatments work at least as well as the current standard treatment (immediate antibiotics by mouth). The Runny Ear STudy (REST) will test if giving an antibiotic eardrop or a delayed antibiotic by mouth is as good as immediately giving antibiotics by mouth for children (without grommets) who have developed AOMd. REST will be a randomised controlled trial - the most reliable method for testing medicines.

We asked parents what concerns them most and what the most parent-child friendly study design would be. Parents told us a wide range of symptoms should be used to assess treatment effectiveness, because they can all cause distress and disrupt family routines. Parents also told us they would not want to leave their child untreated. As a result, REST will use the duration of AOMd symptoms (pain, fever, being unwell, sleep disturbance, discharge, and episodes of distress) as the main test of how good the treatments are, and all children in the study will receive some treatment, either by mouth or as eardrops.

We are a highly experienced group of 'primary care' and 'ear nose and throat' researchers, and we have conducted numerous medicine trials (including the only trial of eardrops for discharge in children with grommets). We think the main challenges to successfully completing this trial will be time and GPs and nurses remembering to recruit. To address these, we will promote the trial (through

advertisements, social media and conferences) to larger GP practices and we will use a state-of-the-art electronic trial platform (called ‘TRANSFoRm’) to make recruitment and follow up as simple as possible. At the end of the trial, we will ensure that the people most likely to benefit hear about the new knowledge, including GPs, nurses, parents, the national press and the National Institute for Health and Care Excellence (NICE).

2. BACKGROUND

Acute otitis media (AOM) is important to children, parents and the NHS for three reasons. Firstly, the infection causes pain and distress to the child, disrupting sleep and family routines. In around 15%, a rise in middle ear pressure bursts the tympanic membrane, releasing the middle ear contents as a discharge (otorrhoea)[1]. Contrary to widespread belief, children with AOM and discharge (AOMd) have similar levels of pain and are more unwell at presentation than children with AOM.[3 4] Moreover, children with AOMd have a worse prognosis, and higher rates of parent-reported pain (at one week), repeat AOM episodes (at 3 months), and hearing problems (at 3 months)[3]. Estimates of parental costs (travel, OTC medicines and lost earnings) vary[5-7], with even the lowest suggesting £4M in England and Wales per annum.

Secondly, AOMd results in health service consultations. Over 90% of UK parents attend primary care for each episode[8], more than for any other common symptom of acute infection, equating to over 150,000 consultations in England and Wales per annum (NHS cost over £3M)[5 6].

Thirdly, more children with AOM and AOMd receive an oral antibiotic in the UK[9] and US[10] than for any other respiratory infection, with three-quarters of GPs prescribing oral antibiotics to at least 80%[11 12]. Our 2015 audit (33 GP practices, 56,251 children) confirmed immediate oral antibiotics is usual care for AOMd: 88% were given oral antibiotics (of which 97% were immediate).

3. RATIONALE

There is strong evidence that children with AOMd benefit from immediate oral antibiotics. The number needed to treat with antibiotics is three to reduce the proportion of children with pain and/or fever at 3 to 7 days compared with placebo/no treatment[4]. As a result, NICE recommends immediate antibiotics should be considered[13]. However, oral antibiotics also cause side effects, are associated with subsequent eczema and hay fever[14], and are associated with population[15] and patient[16] level antimicrobial resistance. The UK's Antimicrobial Resistance Action Plan endorses research to preserve antibiotic effects[17], and our trial proposes to test two interventions that could reduce systemic antibiotic exposure (immediate topical and delayed oral antibiotics), placing this study at the forefront of research to improve antimicrobial stewardship in AOMd.

Research into the clinical effectiveness and economic implications of immediate topical and delayed oral antibiotics is needed since current evidence is limited to showing: (i) the superiority of immediate antibiotics over placebo/no treatment for AOMd symptoms[4] and (ii) the similarity of delayed compared with immediate oral antibiotics in children with AOM (though with reduced antibiotic consumption)[1].

Perforation of the tympanic membrane provides an opportunity to instil antibiotic drops directly into the middle ear, thereby reducing systemic antibiotic exposure. In children with ventilation tubes (from here on 'grommets'), it has been shown that topical antibiotics can reach the infected middle ear against a stream of discharge[18], and that compared with oral antibiotics, they are more effective for otorrhoea duration, AOM recurrence and side effects[18]. This study also showed topical antibiotic to be safe[18] and cost-effective (from a societal perspective)[19]. However, research is needed in children with AOMd without grommets since the tympanic membrane heals quickly and could prevent the drops reaching the middle ear. If topical and delayed antibiotics are shown to be non-inferior, we also need to understand the acceptability of such treatment to clinicians and parents and how to address any barriers to implementation.

Together, this evidence suggests either topical or delayed antibiotics could be at least as effective as immediate oral antibiotics for children with AOMd, and could reduce systemic antibiotic exposure and antimicrobial resistance. We describe a three-arm RCT to investigate the clinical effectiveness and economic implications of topical or delayed antibiotics compared with immediate oral antibiotics, powered for the duration and severity of the symptoms most important to parents, while also investigating adverse events, complications and AOM/AOMd recurrence.

3.1 Existing literature

We reviewed the literature and trials registries in December 2016 and found no relevant published, completed or ongoing studies. Children with bilateral symptoms (e.g. AOMd on one side and AOM on the other, or bilateral AOMd) will be excluded since current National Institute for Clinical Excellence (NICE) guidance recommends immediate oral antibiotics (due to the more severe illness). Children with grommets will be excluded as it has been shown eardrops to be superior to oral antibiotics

3.2 AOMd incidence

Royal College of General Practitioners (RCGP) data[20] show that around 15 children (≥12 months to <16 years) present with AOMd per annum to larger (≥10,000 people registered) GP practices.

3.3 Multisite, open, non-inferiority design

Around 175 primary care sites nationally will maximise generalisability. The open label design will provide 'real-life' estimates of costs (since adherence and re-consultations are influenced by knowledge of treatment). The open label design also reduces trial costs (no placebo, and no Investigational Medicinal Product (IMP) distribution costs to the participating sites). We have selected a non-inferiority design since immediate oral antibiotics are already known to be superior to placebo/ no treatment in AOMd[4], and with fewer systemic side effects[18] and reduced antimicrobial resistance pressures, demonstrating either immediate topical or delayed oral antibiotics are non-inferior would change clinical practice.

3.4 Participants

Children with bilateral symptoms (e.g. AOMd on one side and AOM on the other, or bilateral AOMd) will be excluded since current guidance recommends immediate oral antibiotics (due to the more severe illness)[13]. Children with grommets will be excluded as it has already been shown eardrops are superior to oral antibiotics in children with grommets[18].

3.5 Interventions and comparator

We have selected ciprofloxacin 0.3% as our topical antibiotic since it:

- is active against all common otopathogens[3];
- is non-ototoxic;
- is widely and routinely available in the UK;
- is colourless so will not interfere with assessing otorrhoea;
- will provide complementary evidence to the ZonMw funded trial, which is using an antibiotic-steroid combination.

We have decided to avoid aminoglycoside drops because of ototoxicity concerns. We have proposed delayed oral antibiotics as the second intervention since our previous trials[1 21 22] have achieved significant reductions in oral antibiotic consumption compared with immediate antibiotic prescribing with similar symptom relief. Immediate oral amoxicillin (clarithromycin if penicillin allergic) is the comparator as it reflects usual care and is well tolerated.

3.6 Outcomes

In keeping with previous research[1 4 18 23 24], our PPI group identified the most significant symptoms that should be used to judge recovery as pain, fever, being unwell, sleep disturbance, otorrhoea, and episodes of distress. Primary outcome will be time until all are rated by parents/legal guardians as 'no' or 'very slight' problem (without need for analgesia), assessed using scales shown to be valid and

sensitive to change[1 2]. Secondary outcomes will also reflect their importance to parents/legal guardians[23] and the NHS, and will include:

- time until symptoms are no longer rated 'moderately bad or worse' (also validated)[2];
- AOM and AOMd recurrence at 3 months (antibiotic drops may reduce recurrence)[25];
- parent/ legal guardian-reported hearing loss at 3 months (oral antibiotics have been shown to reduce middle ear effusions)[26] and hearing is important to children's development[27 28].
- analysis of stool samples to assess burden of resistance

Pain and fever will be measured as per the ZonMw trial to facilitate future meta-analysis. It is likely intervention costs and clinical outcomes will be similar across the three groups. However, we propose to explore costs and outcomes from the NHS perspective because we anticipate fewer side-effects and repeat consultations for delayed and topical antibiotics.

3.7 Assessment and management of risk

According to the Medical Research Council (MRC), DH and the Medicines for Healthcare Products Regulatory Agency (MHRA) Risk Adaptive Approaches for CTIMPs, the trial will be categorised as a Type A trial; participants taking part in this trial will be at no higher risk than if they received standard medical care. The medicinal products involved in this study are routinely prescribed within standard care to children within the study age range.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Aim: To investigate the clinical effectiveness and economic impact of immediate topical or delayed oral antibiotics compared with immediate oral antibiotics for symptom duration in children presenting to primary care with acute otitis media (AOM) with discharge AOMd).

4.1 Primary objective

To determine whether either ciprofloxacin 0.3% drops, or delayed oral amoxicillin (clarithromycin if penicillin allergic or other suitable oral antibiotic as chosen by the GP), is non-inferior to current usual care (immediate oral antibiotics) for overall illness duration in children with AOMd presenting to primary care.

4.2 Secondary objectives

1. To estimate the short-term cost-implications of immediate topical or delayed oral antibiotics compared with immediate oral antibiotics from the perspective of the NHS;
2. to compare effects on duration of 'moderately bad or worse' symptoms; parent/legal guardian satisfaction with treatment; and adverse events;
3. to compare hearing loss and AOM/AOMd recurrence rates at 3 months;
4. to understand parent/ legal guardian and clinician views of AOMd trial participation, adherence and satisfaction with allocated treatment.
5. to evaluate the impact of treatment on carriage of antibiotic resistance in the gut

4.3 Outcome measures/endpoints

Primary endpoint/outcome:

Time to resolution of all the following:

- pain;
- fever;
- being unwell;
- sleep disturbance;
- otorrhoea;
- episodes of distress/crying being rated 'no' or 'very slight' problem (without need for analgesia).

Recorded by parents/legal guardians using a validated[1 2] Symptom and Recovery Questionnaire (SRQ) with Research Nurse telephone support.

Secondary endpoints/outcomes:

- duration of 'moderately bad or worse' symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea; episodes of distress/crying;
- appetite and interference with normal activities up to 14 days;
- antibiotic and analgesic use;

- adverse events - diarrhoea, rash, vomiting, serious complications;
- treatment adherence;
- parent/ legal guardian satisfaction with treatment;
- NHS resource use at 14 days;
- repeat AOM and AOMd episodes, serious complications and OM6 hearing questionnaire at 3 months;
- qualitative evaluation of recruitment, medication satisfaction, adherence and follow up.
- analysis of stool sample to assess burden of resistance

5. TRIAL DESIGN

Pragmatic, three-arm, individually randomised (stratified by age <2 vs. ≥2 years), non-inferiority, open trial comparing: (i) immediate topical ciprofloxacin 0.3% drops with (ii) delayed oral antibiotics; or (iii) immediate oral antibiotics. There will be an internal pilot with stop/go criteria (confirming randomisation, treatment adherence and follow up). Economic and qualitative evaluations will be undertaken.

The vast majority of children with AOMd present to, and are managed in, primary care hence our proposed recruitment from primary care sites. Larger (≥10,000) general practice will see around 15 children with AOMd per annum, with Walk-in and out-of-hours centres seeing many more. This means that a large (circa 175) number of primary care sites will be needed to support the study. For a placebo controlled design, the central distribution and tracking of trial medicines over such a large number of sites would be prohibitively expensive. Moreover, to succeed, the trial will need to be easily understood and require fast recruitment procedures easily fitting into routine primary care consultations. In line with the commissioning brief, we have therefore chosen a simple, three-arm design using widely available topical and oral antibiotics, obtainable using standard NHS FP10 prescriptions. The comparator is supported by NICE guidelines[13] and hence familiar to both clinicians and participants. Given current equipoise and that all participants will be receiving active treatment, our PPI advises parents/legal guardians will be willing to support the trial.

To maximise trial efficiency and procedure quality, we will focus on larger (>10,000 registered patients), as well as research active practices. We will:

- use online trial procedures training;
- simplify research governance procedures;
- train and incentivise receptionist teams to steer eligible children into appropriate appointments;
- use the TRANSFoRm trial platform (see section 11) to simplify recruitment procedures[29];
- use standard FP10 NHS prescriptions;
- direct participants to address study procedural questions to the study Research Nurse at the day 1 telephone call.

5.1 Justification for non-inferiority approach

There is good evidence showing that immediate oral antibiotics are superior to placebo for reduction of pain/fever in children with AOMd[4]. As a result, NICE recommends immediate oral antibiotics “be considered”[13]. Our 2015 audit shows current practice complies with NICE guidance - 88% of children with AOMd were given oral antibiotics (of which 97% were immediate, see section 7.2). Since we expect ciprofloxacin 0.3% drops (current NHS 5ml cost = £4.70)[30] will have fewer side effects[18] and less impact on antimicrobial resistance than immediate oral antibiotics (100ml amoxicillin 250mg/5ml NHS cost = £1.36), clinical adoption of the new treatment would be recommended if its clinical effectiveness is at least as good as (non-inferior) current standard therapy[31] and is cost-effective.

Compared with immediate oral antibiotics, we have shown delayed prescribing reduces antibiotic consumption with similar symptom relief for children with AOM[1] (as well as adults with acute sore throat[22] and acute lower respiratory tract infection[21]). Therefore, as with ciprofloxacin drops, we expect delayed antibiotics to result in fewer side-effects and reduced antimicrobial resistance impact, and that it too would be recommended for clinical use if symptom relief was non-inferior.

5.2 TRANSFoRm – an integrated electronic trial management platform

For the past 10 years the US Food and Drug Administration (FDA) and the European Commission have been advocating electronic platforms for clinical trials, whereby the source data is obtained directly from and within the electronic health record (EHR)[32]. Advantages include:

- increased accuracy;
- reductions in data management;
- increased safety (by ensuring trial data is within the clinical record);
- easier trial monitoring; (vi) EHR management of trial workflow, prompts and alerts for recruitment and follow up, and patient reported outcomes[33];
- the use of Clinical Data Interchange Standards Consortium (CDISC) standards for data capture[34] (for more details see section 11).

5.3 Qualitative evaluation

The combination of qualitative and controlled trial methods has long been recommended[35 36]. Qualitative methods are invaluable for understanding the experiences of patients receiving, and staff delivering, interventions[37-39], and have been chosen as the most appropriate means to understand beliefs and perceptions of key medical events[40 41]. To examine the views and experiences of trial recruitment and the different treatments for AOMd, we will conduct in-depth semi-structured qualitative interviews with parents/legal guardians that accept and decline trial participation, and clinicians. These will inform recruitment strategies for this, and future similar trials. Qualitative findings will also help illuminate the perceived effectiveness and acceptability of the different treatment options, explore barriers to their use within, and future uptake outside the trial.

6. TRIAL SETTING

The trial will take place within NHS primary care organisations, defined as providing first-point-of-contact health care and including GP practices and out-of-hours primary care sites (including Walk-in Centres and Out of Hours services) where care is provided by GPs, nurses and paediatricians and supported by the TRANSFoRm platform[29].

7. PARTICIPANT ELIGIBILITY CRITERIA

Children aged ≥12 months to <16 years whose parents/legal guardians are seeking primary medical care for unilateral otorrhoea as the presenting symptom of recent (≤7 days) onset AOM.

7.1 Inclusion criteria

Included **(child must meet all criteria):**

1. Children aged ≥12 months to <16 years;
2. Presenting with recent onset (≤7 days) unilateral AOM with recent onset (≤7 days) otorrhoea currently visible (or seen by parent/legal guardian ≤24 hours);
3. Child attending with parent/legal guardian who is legally able to give consent in person
4. Parent/legal guardian willing and able to administer eardrops;
5. Parent/legal guardian willing, able and available to complete the daily SRQ and received regular telephone calls from the study team.

7.2 Exclusion criteria

Excluded **(if child meets any criterion at the time of entry):**

1. Symptoms/signs suggestive of bilateral AOM/AOMd;
2. Child has symptoms/signs suggestive of serious illness and/or complications e.g. mastoiditis and/or requires immediate hospitalisation;
3. Child requires immediate oral antibiotics (e.g. for another infection or AOMd considered severe);
4. As per NICE guidelines[13], child at high risk of serious complications:
    - Significant immunosuppression;
    - Heart, lung, renal, liver or neuromuscular disease (defined as requiring ongoing inpatient or outpatient care from specialist teams) co morbidities;
    - Trisomy 21 (Down's Syndrome), Cystic Fibrosis or craniofacial malformation such as cleft palate (these children are known to be at higher risk of AOM).
5. Grommet (ventilation tube) in situ in the otorrhoea ear;
6. Currently on oral (for a respiratory tract infection) or topical (in the affected ear) antibiotics;
7. Known allergy or sensitivity to ciprofloxacin, amoxicillin or clarithromycin
8. History of anaphylaxis to other beta-lactam agents
9. Child has taken part in any research involving medicines within the last 90 days;
10. Child has already participated in this trial.

8. TRIAL TREATMENTS

8.1 Interventions

Two interventions:

- immediate ciprofloxacin (0.3%) solution, four drops three times daily for seven days with written advice regarding how to administer drops;

or

- delayed 'dose-by-age' amoxicillin suspension three times daily (clarithromycin twice daily if penicillin allergic or other suitable oral antibiotic as chosen by the GP) for seven days, with structured delaying advice.

All parents/legal guardians will be given standardised information regarding symptom management (i.e. paracetamol/ibuprofen/fluids).

8.1.1 Immediate ciprofloxacin 0.3% drops

The first intervention will be an immediate prescription of ciprofloxacin (0.3%) solution three drops three times daily for seven days. Written advice regarding how to administer the drops will be provided and will include (Appendix 2: Medicines for children advice sheet):

- cleaning the outer ear of discharge that can be easily removed with a tissue;
- tilting the child's head to one side (to approximately 90 degrees) when applying the eardrops;
- maintaining the tilt for a few minutes to improve penetration of the drops;
- tragal pumping (see also http://www.gosh.nhs.uk/medical-information/medicinesinformation/how-to-give-your-child-ear-drops-or-spray/);
- Parents/legal guardians will also receive standardised advice to complete the course.
- In common with many medicines used in children, ciprofloxacin is not licenced for use for this condition. In usual care GPs notify parents of the off label use and the medicine is issued and labelled by the pharmacy with no addition written information. In this trial written information regarding the medicine will be provided by the recruiting clinician.

Table 1: Summary characteristics of ciprofloxacin 0.3%

Characteristic of IMP	**Trial specifics**
IMP: Ciloxan 0.3% w/v eye drops, solution (http://www.medicines.org.uk/emc/medicine/58)	
Marketing Authorisation	Yes (PL00101/0994)

Description, preparation of labelling and supply of IMP	Description: a clear and colourless to pale yellow solution for ocular use. Prescribed in primary care for otic use, off label. Labelling: standard labelling, no specific arrangements required for the trial. Supply: prescribed by clinical staff using standard NHS FP10 prescriptions, which will be dispensed as per routine NHS practice. Written information and instructions regarding the use of the medicine will be provided by the recruiting clinician.
Storage	As per package instructions. Storage conditions in the home will not be monitored.
Known drug reactions or interaction with other therapies	Safety and effectiveness of the drops were determined in 230 children between the ages of 0 and 12. No serious adverse drug reaction was reported in this group. Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. Given the low systemic concentration of ciprofloxacin following topical ocular administration of the product, drug interactions are unlikely to occur. The safety of Ciloxan (common brand of ciprofloxacin) has been tested for otic use. Safety and effectiveness of CILOXAN (a 0.3% eardrop indicated for acute otitis externa) was determined in 139 children between the ages of one and 12 years. No serious adverse events were reported in these patients. Safety and effectiveness in children below 1 year of age has not been established. In clinical trials, the most frequently reported adverse drug reactions were ear pruritus and otorrhoea occurring approximately in1% of patients.
Trial restrictions, medicinal or other contradictions of the IMP, concomitant and contra-indicated medications	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 and the Summary Medicinal Product Characteristics (SmPC) for this drug.
Indications where the drug is licensed and being used	Licensed for ocular use. The use of ciprofloxacin in ears is off-label but evidenced for otic use by Medicines for Children (see appendix 2).

Compliance	Parent/legal guardian -reported patient compliance to the treatment regimen will be assessed in the SRQ.

8.1.2 Justification for dose, frequency and duration of ciprofloxacin drops

Previous trial doses of ciprofloxacin 0.3% drops for the treatment of grommet associated otorrhoea are typically four to six drops given two or three times daily for seven or eight days[42-44] (see also http://www.drugs.com/ciproflaxin-ear-drops.html) We therefore propose four drops three times daily for seven days, which will also match the comparator dose frequency and duration.

8.1.3. Delayed oral antibiotics

As per our previous trials of delayed antibiotic treatment[1 21 22] we propose to match the choice, dose, frequency and duration of our second (delayed oral antibiotic) intervention to the choice, dose, frequency and duration of the immediate oral antibiotic comparator (see section 8.2.1 and 8.2.2). The distinction between this intervention and the comparator is therefore only the advice to delay drug initiation. REST will use the same standardised, structured delaying advice as our previous trials[1 21 22], consisting of:

- giving a post-dated prescription to the parent/legal guardian or asking the parent/legal guardian to return to collect the prescription at the point it is required as per standard delayed prescribing procedure at practice;
- advising the prescription is only 'cashed' at a pharmacy if symptoms worsen or are not starting to improve by the median time symptoms are expected to resolve (4 days)[1 45];
- providing safety netting advice regarding the symptoms that should prompt re-consultation (increasing pain, high temperatures, headaches, irritability or reduced feeding);
- parents/legal guardians will also receive standardised advice regarding how to manage pain, fever and other symptoms.

8.2 Comparator

8.2.1 Immediate amoxicillin

Current usual treatment is an immediate prescription of dose-by-age oral amoxicillin (clarithromycin if penicillin-allergic or other suitable oral antibiotic as chosen by the GP) three times daily for seven days. As with the intervention groups, parents/legal guardians will receive standardised advice to complete the course and how to manage pain, fever and other symptoms. We will use current British National Formulary for Children (BNFfC) recommended dosing, which are:

Amoxicillin dose-by-age:[30]

- 1 to 11 months, 125 mg three times a day for 7 days;
- 1 to 4 years, 250 mg three times a day for 7 days;

- 5 to 11 years, 500 mg three times a day for 7 days;
- 12 to 17 years, 500 mg three times a day for 7 days.

Table 2: Summary characteristics of amoxicillin

IMP: Amoxicillin 125mg/5ml and 250mg/5ml Oral Suspension BP (http://www.medicines.org.uk/emc/medicine/31832) (https://www.medicines.org.uk/emc/product/2137)	
Marketing Authorisation	125mg/5ml (PL06453/0021) 250mg/5ml (PL06453/0022)
Description, preparation of labelling and supply of IMP	Description: yellow granular powder for oral suspension indicated for the treatment of infections in adults and children including acute otitis media. Labelling: standard labelling, no specific arrangements required for the trial. Supply: prescribed by clinical staff using standard NHS FP10 prescriptions, which will be dispensed as per routine NHS practice
Storage	As per package instructions. Storage conditions in the home will not be monitored.
Known drug reactions or interaction with other therapies	The most commonly reported adverse drug reactions are diarrhoea, nausea and skin rash.
Trial restrictions, medicinal or other contradictions of the IMP, concomitant and contra-indicated medications	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 and the SmPC for this drug.
Compliance	Parent/legal guardian -reported patient compliance to the treatment regimen will be assessed in the SRQ.
IMP: Amoxicillin 500mg Capsules BP (http://www.medicines.org.uk/emc/medicine/25942)	
Marketing Authorisation	(PL20075/0264)
Description, preparation of labelling and supply of IMP	Description: hard capsule, scarlet body, ivory cap indicated for the treatment of infections in adults and children including acute otitis media.

	Labelling: standard labelling, no specific arrangements required for the trial. Supply: prescribed by clinical staff using standard NHS FP10 prescriptions, which will be dispensed as per routine NHS practice
Storage	As per package instructions. Storage conditions in the home will not be monitored.
Known drug reactions or interaction with other therapies	The most commonly reported adverse drug reactions are diarrhoea, nausea and skin rash.
Trial restrictions, medicinal or other contradictions of the IMP, concomitant and contra-indicated medications	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 and the SmPC for this drug.
Compliance	Parent/legal guardian -reported patient compliance to the treatment regimen will be assessed in the SRQ.

8.2.2 Clarithromycin

Smith's 2010 study showed 84% of children with AOMd received an immediate prescription for amoxicillin with a further 5% receiving oral erythromycin, 3% topical gentamicin and 8% receiving no antibiotic.[3] Our 2015 audit (33 GP practices, 56,251 children) confirmed immediate oral antibiotics as usual care for AOMd: 88% were given oral antibiotics (of which 97% were immediate), with amoxicillin the most widely prescribed antibiotic. Invariably, UK primary care practice is to prescribe amoxicillin 'dose-by-age'. We will use latest BNF for Children[30] prescribing guidance to prevent under- and overdosing the oldest and youngest children[46]. Clarithromycin is a commonly used and well-tolerated alternative for penicillin-allergic children and we will include similar dosing advice. GPs may choose an alternative antibiotic if indicated due to specific patient characteristics, e.g. intolerance to both alternatives or interactions.

Dose-by-weight/dose-by-age[30]:

- Under 8 kg, 7.5 mg/kg twice a day for 7 days;
- 8 to 11 kg, 62.5 mg twice a day for 7 days;
- 12 to 19 kg, 125 mg twice a day for 7 days;
- 20 to 29 kg, 187.5 mg twice a day for 7 days;
- 30 to 40 kg, 250 mg twice a day for 7 days;
- 12 to 17 years, 250 mg twice a day or 500 mg twice a day for 7 days.

Table 3: Summary characteristics of clarithromycin

IMP: Clarithromycin 125mg/5ml suspension (http://www.medicines.org.uk/emc/medicine/23012)	
Marketing Authorisation	Yes (PL 04416/0609)
Description, preparation of labelling and supply of IMP	Description: white to beiger granules for oral indicated in adults, adolescents and children, 6 months to 12 years, for the treatment of the following acute and chronic infections, including acute otitis media. Labelling: standard labelling, no specific arrangements required for the trial. Supply: prescribed by clinical staff using standard NHS FP10 prescriptions, which will be dispensed as per routine NHS practice
Storage	As per package instructions. Storage conditions in the home will not be monitored.
Known drug reactions or interaction with other therapies	Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The most commonly reported adverse drug reactions are: abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These reactions are usually mild in intensity.
Trial restrictions, medicinal or other contradictions of the IMP, concomitant and contra-indicated medications	Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. 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 and the SmPC for this drug.
Compliance	Parent/legal guardian -reported patient compliance to the treatment regimen will be assessed by a series of questions in the SRQ at day 14.
IMP: Clarithromycin 250mg film coated tablets (http://www.medicines.org.uk/emc/medicine/33774)	
Marketing Authorisation	Yes: PL 04569/1212
Description, preparation of labelling and supply of IMP	Description: yellow, oval, biconvex film coated tablet indicated for treatment of infections caused by clarithromycin-susceptible organisms.

	Labelling: standard labelling, no specific arrangements required for the trial. Supply: prescribed by clinical staff using standard NHS FP10 prescriptions, which will be dispensed as per routine NHS practice.
Storage	As per package instructions. Storage conditions in the home will not be monitored.
Known drug reactions or interaction with other therapies	Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The most commonly reported adverse drug reactions are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These reactions are usually mild in intensity.
Trial restrictions, medicinal or other contraindications of the IMP, concomitant and contra-indicated medications	Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age. 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 and taking account of SmPC.
Compliance	Parent/legal guardian -reported patient compliance to the treatment regimen will be assessed in the SRQ.
IMP: Clarithromycin 250mg/5ml suspension (http://www.medicines.org.uk/emc/medicine/26873)	
Marketing Authorisation	Yes: PL 04416/0610
Description, preparation of labelling and supply of IMP of labelling of IMP	Description: white to beige granules for oral suspension indicated in adults, adolescents and children, 6 months to 12 years, for the treatment of the following acute and chronic infections, including acute otitis media. Standard labelling, no specific arrangements required for the trial. Supply: prescribed by clinical staff using standard NHS FP10 prescriptions, which will be dispensed as per routine NHS practice.
Storage	As per package instructions. Storage conditions in the home will not be monitored.

Known drug reactions or interaction with other therapies	Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The most commonly reported adverse drug reactions are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These reactions are usually mild in intensity.
Trial restrictions, medicinal or other contradictions of the IMP, concomitant and contra-indicated medications	Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. 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 and taking account of SmPC.
Compliance	Parent/legal guardian -reported patient compliance to the treatment regimen will be assessed in the SRQ.

8.3 Risks associated with trial interventions

The trial IMPs are classified as 'Category A: comparable to risk of standard medical care'. Amoxicillin and clarithromycin are standard prescription antibiotics and will be prescribed with standardised dose, frequency and side effect information. Ciprofloxacin, used off-label in this trial will be prescribed with an information sheet explaining the off-label use of the drug and dose, frequency and side effect information. This replicates usual care for off label medicines with the provision of an additional written information sheet. Trial participants will be provided with a telephone number for the trial team to contact in the instance of requiring advice. Trial participants will also be free to contact their GP.

8.4 Compliance with trial medicinal products

Compliance with each of the trial drugs will be measured via the SRQ on a daily basis. We will not be assessing compliance beyond this since this is an open, pragmatic trial to test effectiveness as opposed to efficacy with emphasis on testing the treatment decision.

8.5 Repeat consultation for AOM/d

If, following treatment for AOM/d within the parameters of the trial, the participant consults their GP for recurring symptoms, subsequent consultation(s) is considered usual care and the child is not permitted to re-enter the trial. Recurrent consultation for AOM/d and treatment outside of the trial will be captured by the PCNR (Primary Care Notes Review) at 3 months.

9. TRIAL PROCEDURES

9.1 Recruitment identification, screening and recruitment

Children will be recruited from primary care where the vast majority of children with AOM/d are managed. Generalisability will be maximised by encouraging recruiting practices to invite all eligible patients; success of this will be measured by asking sites to record the characteristics of patients/reasons where this is not possible, using the TRANSFoRm platform.[29] The TRANSFoRm platform will use the READ/Snomed CT codes for research to tag all data entries in the EHR from screened/ineligible, screened/eligible, consented, randomised, followed up and withdrawals.

The initial assessment and diagnosis of AOM/d will be according to routine clinical practice.

Parents/legal guardians will be asked about baseline symptoms, similar to usual care. Following informed consent participants will be randomly allocated (1:1:1) to receive treatment as usual (oral antibiotics) or ciprofloxacin drops or a delayed (oral antibiotic) prescription.

9.2 Informing participants of the risks and anticipated benefits

Parents/legal guardians and children will be informed of the potential risks and benefits of participating in the trial in age appropriate participants information sheets. Parents/legal guardians and children will also have the opportunity to discuss these further and ask any questions of their GP in their appointment, or to contact the study team.

9.3 Consent

Participation will be invited by recruiting site staff and will be entirely voluntary, with parents (or those legally allowed to consent for children, (http://www.hra-decisiontools.org.uk/consent/principles-children-EngWalesNI.html) being given full information regarding what trial participation involves, their right to withdraw and research dissemination plans. Consent forms will be generated within the TRANSFoRm system and populated with relevant details, i.e. study ID and contact details. Full written consent will be obtained from those legally allowed to consent on children's behalf. Assent will be expected to be obtained from all children over the age of 6 wherever possible, with written justification of reasons if assent is not obtained.

All study employed research staff with participant contact will have passed Disclosure and Barring checks.

Non-English-speaking parent/legal guardians and children will not be invited to participate since the invitation to participate, consent and issue of prescription takes place within the GP consultation. It would not be feasible to seek translation facilities or patient-facing documents in an alternative language within the standard 10-minute GP consultation period. Signed and completed consent and contact details will be sent to the lead study centre via either fax or secure email.

9.4 The randomisation scheme

Following eligibility confirmation and consent, children will be randomised, stratified by age (<2 years and ≥2 years since children <2 years experience longer illness duration)[4]. Two randomisation lists will be generated by the BRTC as per the stratification[29]. Blocks of 12 will be used for allocation (4 in each arm), since most practices will recruit one or two patients only. The sequence will be supplied to the TRANSFoRm platform to be allocated to each successive participant recruited. A system for checking the correct randomisation allocation will be built in to the TRANSFoRm platform and treatment allocation will be checked in the patient symptom questionnaire. Clinicians will not be able to determine treatment allocation pre-randomisation.

Randomisation will be triggered by the recruitment process within the TRANSFoRm application. The GP will be notified of the randomisation allocation via TRANSFoRM.

9.5 Blinding

Once the allocation is revealed, neither clinicians nor the child participant or their carer will remain blind to their allocated treatment. Codes will be assigned to the database, which will preserve blinding of study personnel. The senior statistician will remain blind to knowledge of which treatment is represented by each treatment code until final results have been shared with the Data Monitoring Committee.

9.6 Emergency Unblinding

Emergency unblinding will not be necessary in this trial since it is an open study.

9.7 Baseline data

Baseline data will be collected at day 1 (the day of recruitment) by the recruiting clinician and parent/legal guardian with study nurse support. Eligibility criteria, parent/legal guardian -reported symptoms and brief clinical examination findings will be recoded using the embedded case report from in the electronic health record, managed by the TRANSFoRm platform[29]. Once the signed consent and contact details forms have been received by the REST research nurse, they will make contact by telephone on day 1 to address any questions or concerns that the parent/legal guardian may have about the trial, advise in accessing and completing the SRQ via the TRANSFoRm platform. If the parent/legal guardian has chosen to complete the SRQ on paper the REST research nurse will directly enter the data into TRANSFoRm.

9.8 Frequency and duration of follow-up

After recruitment and randomisation, parents/legal guardians will be asked to complete a daily SRQ recording the symptoms identified by parents/legal guardians as important. The SRQ will be provided in electronic format (either for web or iOS/Android app) via the TRANSFoRm platform or in a paper version to allow for parental/carer preference. This will provide a daily record of symptom burden and will be completed for up to 14 days. The primary outcome will be collected using SRQ with research nurse telephone call (we have achieved <20% primary outcome attrition using this method in other similar trials[1 47-49]). A total of 5 telephone calls will be made:

- on day 1 - where possible on the day of recruitment or within 24 hours to check they are happy with participation in the trial, to ensure the parent/legal guardian is confident about what is required to participate in the trial and agree the times of future calls;
- on day 3 to oversee primary outcome data collection;
- at 7 days to oversee further outcome collection;
- on day 10 to oversee further outcome collection
- a final call at 14 days to oversee final outcome collection and stool sample.

Telephone calls will be made on weekdays; calls that are due over a weekend will be made on the next working day.

In combination, the TRANSFoRm system and parents/legal guardians in the SRQ will record the following data on the evening of days 1-14:

- the daily presence and severity of AOMd symptoms (until cessation of all symptoms for two consecutive days without need for analgesia): pain, fever, being unwell, sleep disturbance, otorrhoea, episodes of distress/crying, appetite and interference with normal activities;
- daily measures of compliance with the study medicine;
- use of analgesic/antipyretics in conjunction with the study medicine obtained either by prescription or over-the-counter (SRQ);
- occurrence of adverse events, including otitis externa, rash, fungal ear infections, diarrhoea, rash, vomiting and serious AOM complications;
- overall satisfaction with the trial treatment that the child received.

On day 7 and day 14 telephone calls, information on the use of healthcare resources including information about primary care contacts, use of 111 and walk-in centres, and hospital services will be obtained.

At month 3, use of hospital services will be collected by review of the patients' EHR.

The final questionnaire will be sent three months after randomisation either electronically (web or iOS/Android app) via the TRANSFoRm platform or paper questionnaire. The questionnaire will ask parent/legal guardian-reported hearing loss at 3 months measured using the OM6[50] questionnaire.

Parents/legal guardians reporting long-term symptoms (ongoing at day 14) will be asked for their willingness to receive a symptom follow-up call from the study team at 6 weeks post-recruitment.

9.9 Withdrawal criteria

Parents/legal guardians 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/legal guardians 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/legal guardians who withdraw their children from the trial will be asked if they are still willing to provide follow-up data via the SRQ.

Furthermore, we intend to conduct telephone interviews with parents/legal guardians who decide to decline participation or withdraw (n=15). If a child is withdrawn, the reason for and type of withdrawal will be documented in the electronic Case Report Form (eCRF). For example, type of withdrawal may include:

- trial use of baseline (eCRF) data;
- use of trial medication;
- completing SRQ;
- receiving telephone calls, letters, email or texts to support SRQ;
- review of their primary care record;
- completion of the final questionnaire at 3 months;
- any combination or all of the above.

The Principal Investigators (PI) 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 TRANSFoRm system via a specific 'withdrawal form' and coded in the EHR with a specific READ/Snomed CT code. 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.

Recruitment will continue until the required number of follow-up datasets are received, thereby replacing any children who have been withdrawn before SRQ 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.

9.10 Storage and analysis of microbiological clinical samples

At the 7-day telephone call, the research nurse will remind parents/legal guardians of the stool sample collection at day 14. Parents/legal guardians will be sent a pack containing instructions, a sample collection container, a secondary container with absorbent material e.g. SpeciSafe from Alpha Labs SH060055 and finally a UN 3373 'MailTuff™' envelope and the return addressed (to the Research Laboratory at Southmead Hospital, North Bristol NHS Foundation Trust) at the end of week one. A similar pack will be sent at 3 months. Parents/legal guardians will return the samples using the MailTuff™ envelope using standard Royal Mail postal services.

On receipt at North Bristol NHS Foundation Trust, samples will be diluted in saline (approx. 10% Wt:Vol) and plated onto MacConkey Agar to allow isolation of *E.coli* from the faecal flora. Simultaneously, non-selective media containing the study antibiotics will be used to assist in the identification of resistant organisms. Unique isolates morphologically consistent with *E.coli* will be identified by Matrix-assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) and up to six

E.coli isolates per patient will be stored for subsequent minimum inhibitory concentration (MIC) testing by agar dilution to amoxicillin, clarithromycin and ciprofloxacin. The faecal dilution will also be stored for the duration of the study and the discarded. Results will be presented categorically based on whether or not the subject had an *E.coli* isolate resistant to each of the study antibiotics.

Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

9.11 End of trial for participants

Participants' involvement in the trial will end 3 months after entry when the participant's parent/legal guardian has completed the final questionnaire and stool sample.

9.12 Payment to participants

On completion of the SRQ parents/legal guardians will receive a £10 high street shopping voucher and a £5 voucher on completion of the stool sample. Parents/legal guardians will receive a further £5 shopping voucher for completion of the second stool sample at month 3. Children aged 10-16 will receive a £10 voucher for participating in the trial and children under 10 will receive a piggy bank. Parents/legal guardians, who participate in a qualitative interview, will also be offered a £10 high street shopping voucher as a thank you for their time.

10. PHARMACOVIGILANCE AND SAFETY REPORTING

10.1 Operational definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product that is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Term	Definition
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

10.2 Severity classifications

Mild event:	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event:	An event that prevents normal everyday activities.

10.3 Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is 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 intervention, 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 intervention, is reasonable and the event is more likely explained by the intervention than any other cause.

Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

10.4 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).

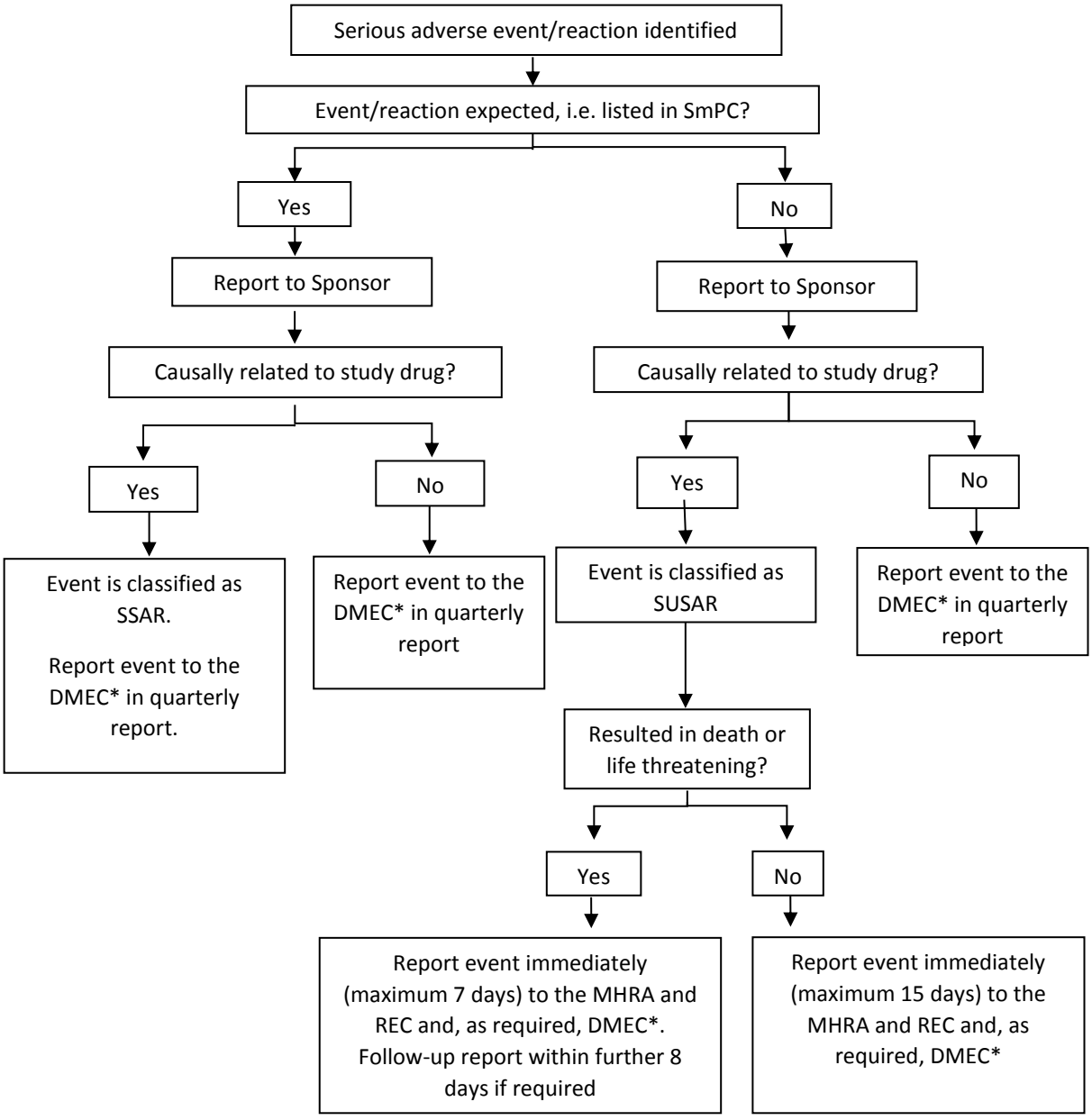


Figure 1: Event reporting flowchart

10.4.1 All adverse events

All AEs will be recorded by the Chief Investigators (CI) from the time a signed and dated informed consent form is obtained until completion of the patient follow-up at 14 days after randomisation. Adverse events described in the SmPC associated with the trial drug will be monitored and recorded as non-reportable.

If a Responsible Clinician or other member of the research team becomes aware that a trial-related SAE has occurred beyond the 14-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. UHBristol, on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by the CI.

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

All emerging pharmacovigilance data, which may be related to activities carried out by the IMP will be notified to the supplier via the MHRA Yellow Card scheme: www.mhra.gov.uk/yellowcard.

10.4.2 Serious adverse events (SAEs)

All SAEs must be reported to the UHBristol 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 CI should also be informed.

All SAEs that have not been resolved by 28 days following consent 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 (this must be documented in the eCRF).

10.4.3 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 UHBristol, on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the section 4.8 of the Summary of Product Characteristics. UHBristol 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 UHBristol, 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.

10.4.4 'Expected' adverse reactions and events

Any 'common' symptom, side effect or adverse event listed section 4.8 of the Summary of Product Characteristics will not be regarded as unexpected. See section 7 for the common effects associated with use of the trial IMPs.

Common signs and symptoms of AOM/AOMd:

- painful and/or hot ears;
- discharge from ears;
- red ears;
- fever;
- high temperature;
- hearing loss or muffled hearing;
- malaise;
- irritability, crying, poor feeding, restlessness;
- coryza/rhinorrhoea;
- vomiting.

Complications of AOM/AOMd include:

- progression to chronic suppurative otitis media occur;
- labyrinthitis, meningitis, intracranial sepsis or facial nerve palsy are very rare and occur in less than 1 in 1,000;
- recurrent episodes may lead to scarring of the eardrum with permanent hearing impairment, chronic perforation and otorrhoea, cholesteatoma or mastoiditis;
- in a small child with a high temperature there is a risk of febrile convulsions;

- rare complications include:
  - petrositis;
  - acute necrotic otitis;
  - otitic hydrocephalus (hydrocephalus associated with AOM, usually accompanied by lateral sinus thrombosis but the exact pathophysiology is unclear);
  - subarachnoid abscess;
  - subdural abscess;
  - sigmoid sinus thrombosis.
- rarely, systemic complications can occur, including:
  - bacteraemia;
  - septic arthritis;
  - bacterial endocarditis.

  Rare complications and systemic complications will constitute SAE if they lead to hospital admission.

10.5 Treatment stopping rules

The trial may be prematurely discontinued by the Sponsor, CI, Regulatory Authority or Funder on the basis of new safety information or for other reasons given by the DMEC/TSC or Research Ethics Committee (REC).

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 followed up according to the protocol within the limits of the closedown schedule.

10.6 Overdose

Adherence to the dosing schedule will be measured in the SRQ. Since this data is collected retrospectively and once the course of treatment has concluded, participants demonstrating a potential overdose on the SRQ will not be withdrawn from the trial. Their data will be included in the main analysis according to the intention-to-treat principle but excluded from the per-protocol analysis (see section 10.4): numbers of participants for whom this is relevant will be reported to the DMEC.

No toxic effects are to be expected with an otic overdose of Ciloxan product or with accidental ingestions of the contents of one bottle ((http://www.medicines.org.uk/emc/medicine/58).

No definition of amoxicillin and clarithromycin overdose is reported in the SmPC. Parents of children suspecting that they have administered an overdose of these medicinal products are instructed to contact their GP as soon as possible per the patient information leaflet.

10.7 Notification of deaths not constituting a SAR or SUSAR

All deaths, including deaths deemed unrelated to the IMP, will be reported to the sponsor within 24 hours of the research team receiving the information.

10.8 End of safety reporting period

SAEs will be recorded up to the end of the participants' trial involvement – to day 28.

10.9 Development safety update reports

The Sponsor will provide Development Safety Update Reports (DSURs) once a year throughout the clinical trial, or as necessary, to the Competent Authority (CA) – the MHRA and where relevant the REC.

11. STATISTICS AND DATA ANALYSIS

11.1 Sample size

Our previous trial compared immediate with delayed antibiotics.[1] Children with AOMd took a median of 3 days (IQR 2,4) to achieve the REST primary outcome. Our PPI advised a 1.25 day non-inferiority margin (equivalent to an absolute difference in cure rate of 19.5% at 3 days). A two-group non-inferiority trial normally assumes 2.5% one-sided Type I error. Using 1.25% Type I error to detect non-inferiority for two comparisons with 90% power, complete outcome data needed for 106 per arm; 399 with 20% attrition.

11.2 Primary outcome

In keeping with previous research[1 4 18 23 24], our PPI group has identified the most significant symptoms that should be used to judge recovery as: pain, fever, being unwell, sleep disturbance, otorrhoea, and episodes of distress. They also reported that they would regard their child as 'recovered' when they rated all of these symptoms as 'no' or 'very slight' problem. Our primary outcome will therefore be the time to resolution of all pain, fever, being unwell, sleep disturbance, otorrhoea, and episodes of distress/crying being rated 'no' or 'very slight' problem by parents/legal guardians without need for analgesia. We will use a validated[2] SRQ, known to be sensitive to change[1], similar to SRQs we have used our previous studies[1 47-49], where we have achieved >80% diary completion rates with Research Nurse telephone support. The presence and severity of each symptom will be recorded daily using a Likert scale: zero 'normal/none'; one 'very slight problem', two 'slight problem'; three 'moderately bad'; four 'bad'; five 'very bad'; and six 'as bad as it could be'. Symptoms will be recorded until all symptoms have been rated zero for two consecutive days, or day 14, whichever comes soonest (our research has shown that the symptoms of AOM have resolved in 90% children by day 8)[45]. Symptoms will be recorded via the TRANSFoRm platform[29] (or paper) with real-time monitoring of data completion. We will ask parents/legal guardians to complete the daily symptom diary in the evening of each day to cover the previous 24 hours.

11.3 Secondary outcomes

Secondary outcomes will also reflect their importance to parents[23] and the NHS. Those recorded in the first 14 days (on the SRQ) will include:

- duration of 'moderately bad or worse' symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea; episodes of distress/crying;
- adverse events (diarrhoea, rash, vomiting and severe complications at days 7 and 14);
- parent/legal guardian satisfaction with treatment (day 14);
- treatment adherence and analgesic use to symptom resolution up to day 14 (SRQ);
- details of NHS resource use at day 7 and 14 on the SRQ;
- analysis of stool sample to assess burden of resistance.

11.4 Analysis

At the end of the trial, data will be transferred from TRANSFoRm to the Bristol Randomised Trials Collaboration (BRTC, the Bristol CTU). 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 other continuous variables, and numbers with percentages for categorical variables. Data will be transferred as appropriate if the DMSC require it and for monitoring of data quality.

Our primary outcome will consist of the time until all symptoms are rated 'none' or 'very slight' and will be compared between treatment arms on an intention-to-treat basis. We will produce Kaplan-Meier survival curves for the three treatment arms and the difference in median days to resolution of symptoms between children allocated to immediate antibiotics and those allocated to each of the other treatment arms will be estimated with 95% confidence intervals, using Cox's proportional hazards model. Since most children's symptoms will be resolved by the end of follow-up, we will additionally apply an accelerated failure time model, allowing us to estimate directly the effect of allocated treatment on length of time to symptom resolution: a model previously recommended for studies of resolution of infectious disease[51]. We will also compare the proportions reporting complete (or to 'very mild') symptom resolution at 3 days and estimate the absolute difference. These will enable us to judge whether non-inferiority has been demonstrated[52],in particular whether the lower limit of the one-sided 97.5% CI is within the maximum unimportant difference. Using regression models, we will also carry out an analysis, which adjusts for important variables collected at randomisation (covariates), such as baseline pain. To assess the potential effects of missing data either for covariates or for the outcome, multiple imputation methods will be utilised in a sensitivity analysis.

We will also carry out a per protocol (PP) analysis. In a non-inferiority trial, PP analysis would be considered conservative compared with an intention-to-treat (ITT) analysis, since it might be harder to demonstrate non-inferiority. While our ITT analysis will be the single most important benchmark by which non-inferiority (or otherwise) is established, evidence for non-inferiority will be considered strongest if demonstrated both in ITT and PP analyses.

We will assess the degree to which treatment differences might differ by age group (<2 and ≥2 years), by adding a treatment x age interaction. While the study will not carry sufficient power to demonstrate non-inferiority for each age group separately, we will note any significant differences in effect size. Among secondary outcomes, time during which symptoms are rated no longer 'moderately bad or worse' will be analysed with similar survival analyses as for our primary outcome. Binary outcomes (including adverse events or recurrence of AOMd) will be analysed using logistic regression analysis while semi-continuous scores such as parental/carer satisfaction and hearing loss at 3 months will be analysed using ordinary linear regression where these variables conform reasonably closely to a Normal distribution: otherwise negative binomial regression analysis or other suitable alternatives will be chosen.

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

11.5 Measuring and mitigating threats to external and internal validity

11.5.1 External validity

Generalisability will be maximised by asking clinicians to invite all potentially eligible children to participate.

As we have with previous studies[48 53],where study invitations are declined, parents/legal guardians will be asked for basic details of their children (age, gender and global illness severity) which will be recorded via the TRANSFoRm platform, as well as a reason for declining participation.

11.5.2 Internal validity

Confounding: Concealed randomisation stratified by age (<2 vs. ≥2 years) will ensure treatment groups are similar with respect to age, and should achieve balance in both measured and unmeasured potential confounders.

Treatment crossover and adherence: In an open label trial, which we consider necessary for REST, there is a possibility that children will not be given the treatment to which they are randomised. There is no single agreed threshold at which patients are regarded as 'adherent' (and it is likely to vary between diseases and medication classes), but 80% is often regarded as reasonable.[54] Higher levels of adherence than this were achieved in a previous open trial of oral vs. topical antibiotics for children with grommets and ear discharge[18]: 88% and 93% fully adhered to oral and topical antibiotics respectively. Minimising treatment crossover will be a key clinician-training element, and the TRANSFoRm platform will minimise crossover by guiding clinicians to issue the 'correct' treatment. Finally, treatment adherence will be closely monitored (using the SRQ) and has been included as a key performance measure in our internal pilot.

11.5.3. Performance, measurement and attrition bias

Although participants will not be blinded to their treatment allocation, given current treatment equipoise and the fact that all participants will receive active antibiotic treatment, we do not believe parent/legal guardian knowledge of treatment allocation will influence their perception of symptoms. Members of the Trial Management Group and the statistical team will remain blind (except in the instance that the DMC require interim data) to treatment allocation until analyses have been completed. REST will use outcome measures successfully used in our previous studies[1 47 49], and shown to be valid[2] and sensitive to change[1 47 49]. We regard 80% follow up as the absolute minimum, but with online data collection and telephone support from an experienced research nurse, we usually achieve closer to 90% follow up for our SRQ-based primary outcomes[1 47 49].

11.6 Economic evaluation

The primary economic evaluation will explore the relationship between cost and outcome for the three treatments for AOMd (immediate topical, delayed oral and immediate oral antibiotics) from an NHS perspective at 14 days post-randomisation. This will take the form of a simple comparison of NHS costs and outcomes over a period of two weeks from randomisation.

A secondary cost analysis will evaluate the difference in NHS secondary care costs between the trial arms for the three months following randomisation.

All resources will be valued using unit costs from established sources. These will include Unit Costs of Health and Social Care[55] for primary and community care, NHS Reference Costs[56] for hospital care and the BNFC[30] for prescribed medication.

Differences in NHS resources and costs between the arms will be analysed initially using Ordinary Least Squares (OLS) regression. The distribution of residuals from the regression models will then be examined and a decision will be made as to whether OLS is appropriate or another type of regression model should be considered (e.g. Generalised Linear Models (GLM)).

A cost consequence analysis will then be conducted in which the costs to the NHS of the three treatments at 14 days post-randomisation will be compared with the primary clinical outcome. Areas of uncertainty in assumptions will be subjected to sensitivity analyses to test the robustness of the results.

12. DATA MANAGEMENT

12.1 TRANSFoRm Platform

The TRANSFoRm platform encapsulates certain features of a clinical trial management system by interacting with the GP's EHR. The tool provides automatic eligibility checking, part-filling of eCRFs, and study workflow management and has been validated against Good Clinical Practice guidelines.

All REST quantitative data will be collected using such a system – namely, the EU FP7 funded TRANSFoRm Program (www.cdisc.orgtransformproject.eu)[29]. TRANSFoRm uses a Data Node Connector (DNC) to integrate with primary care EHR electronic medical records (also increasingly used in Walk-in and Out-of-Hours centres), ensuring data validity and accuracy, and facilitating the nationwide engagement of the large number of primary care sites needed for REST. An additional module enables Patient Reported Outcome Measures (PROMs) to be collected via web and smartphone (iOS, Android). The system has a full provenance trail and is fully GCP/MHRA validated. Each Data Node Connectors (DNC) has been constructed with the participation of the system vendor. The basic components of the system are: (i) a Study System (TSS) that manages projects, sites and workflow; (ii) middleware that manages authentication and messaging; (iii) a system for triggering and storing PROMs; (iv) a DNC specific to each EHR system, that links clinical systems to the TSS via their Application Programming Interface (API); and (v) an online back-up data collection system. For REST, a set of xml files will be developed, specifying the data elements to be captured, and their linkage to the TRANSFoRm Clinical Data Information Integration Model (CDIM), structured according the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Model (ODM), and the timeline according to the CDISC Study Data Model (SDM). Further ODM files containing questions for the PROMS will be developed, and structured searches will be developed for any data elements that are to be pre-populated by the data in the EHR. See Figure 1.

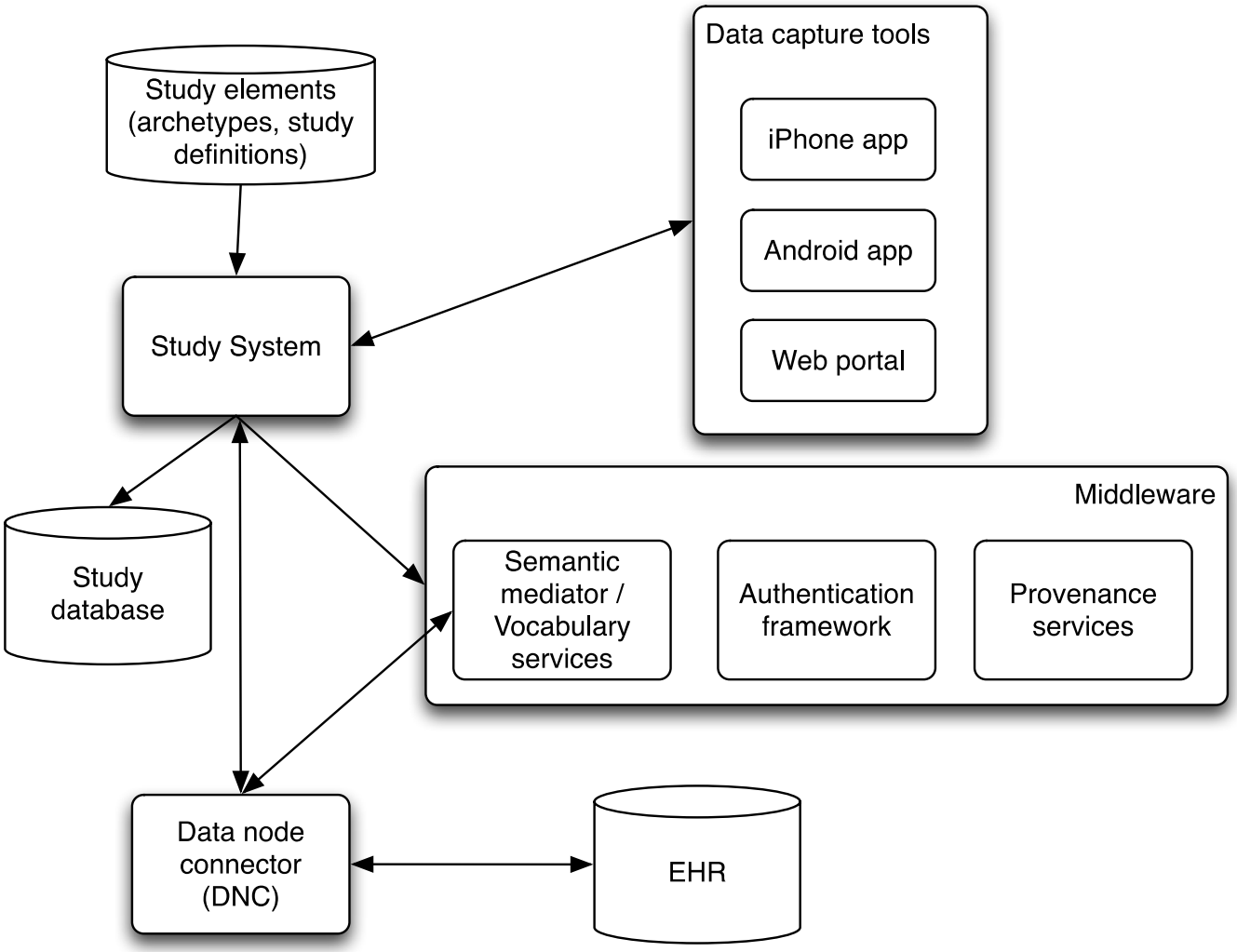


Figure 2: Schematic of the TRANSFoRm system architecture

12.2 Source documents and data collection and source document identification

12.2.1 Source data and documents

Source data will comprise:

- consent and assent forms;
- randomisation status;
- participants' TRANSFoRm profile;
- SRQ for days 1-14;
- OM-6 and health resource use at days 7, 14 and month 3;
- stool sample analysis at day 14 and month 3;
- EHR;
- qualitative interviews.

12.2.2 Data collection

Table 4: Participant data collection at trial timepoints for intervention and control trial participants

Data	Baseline	Days 1-13	Day 14	Month 3
Consent and assent (if applicable)	•			
Randomisation	•			
SRQ		•	•	
EHR and TRANSFoRm profile	•			•
Stool sample			•	•
Health resource use		•	•	•
OM-6				•
Qualitative interview for decliners		•		
Qualitative interview for trial parents/legal guardians			•	

Data collection will include the following elements:

- consent and assent to the trial and baseline information collected prior to randomisation. Baseline information will be recorded in the participants' TRANSFoRm profile via their medical record;
- randomisation status of the participant recorded via the TRANSFoRm profile;
- parent/legal guardian completed SRQ on days 1-14 as one document;
- trial specific data required to answer the primary and secondary outcomes (see section 10.2 and 10.3) via a READ/Snomed CT code search of the TRANSFoRm profile in conjunction with a hand review of EHR;
- results of the analysis of participants stool sample at day 14 and month 3;
- OM-6 at month 3;
- health resource use at days 7, 14 and month 3. Health resource data will be collected via TRANSFoRm (days 7 and 14) and by hand review of EHR (month 3).
- interviews with parents/legal guardians that accept and decline trial participation.

12.3 Case report forms

In this instance, the participants' TRANSFoRm portfolio forms the eCRF. Data will be stored directly to the eCRF in real-time, during the consultation. Validation of data entered will be built into TRANSFoRm, by limiting the fields that GPs are completing in the eCRF to specified value ranges and data types. Completion of the form will be guaranteed because only complete forms will be activated for submission and GPs will be prompted to complete missing data.

12.4 Data handling, archiving and retention

Data Custodian: Head of School, Bristol Medical School, University of Bristol.

The validated clinical database (TRANSFoRm), trial management database (REDCap) and randomisation system will be designed so as to protect patient information in line with the Data Protection Act 1998. Data will not transfer from the GP system to TRANSFoRm until the parent/legal guardian has consented to theirs and their child's participation. Trial staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centres. Data will be anonymised as soon as it is practical to do so in line with the Data Protection Act 1998. The study participants will be identified only by a patient ID number on the C/eCRF (both on the paper and web-based forms). Participants contact details will be stored on the secure REDCap system based at the University of Bristol.

All study documentation will be retained in a secure location during the conduct of the study. 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.

To comply with the fifth Principle of the Data Protection Act 1998 (this process will be reviewed and updated accordingly with any updates to the guidelines), personal data will not be kept for longer than is required for the purpose for which it has been acquired. Data will be held in compliance with the sponsor's standard operating procedures. Formal trial specific SOPs will be developed to detail each element of the data handling procedure.

All non-essential data will be wiped upon completion of the study.

12.4.1 Incoming electronic data transfer

At the end of trial period, data collected in TRANSFoRm will be transferred to the University of Bristol via secure transfer using the SFTP protocol. Successful transfers will be acknowledged via e-mail to TRANSFoRm. The data will be anonymised, since data for the purposes of research and patient contact details are stored separately in the TRANSFoRm system and patients are identified by a unique study ID. An interim transfer of data will be scheduled after the first 10 participants have been recruited to test and validate the data transfer system.

Results of the microbiology of the stool samples at day 14 and three months will be transferred to the University of Bristol via a secure data transfer mechanism to be agreed between the two parties.

A study specific Data Management Plan (DMP) will be developed for the REST trial outlining in detail the procedures that will be put in place to ensure that high-quality data are produced for statistical analysis.

All electronic data files will be saved in a secured computer and to a password-protected University of Bristol network space, in accordance with the University of Bristol's data security policies.

12.4.2 Hard copy data transfers

All patients will be consented using paper consent forms, pre-numbered by the TRANSFoRm system with the Patient ID number. Consent forms will be scanned and linked to the patient's medical record by site staff and sent by secure fax/email to the Bristol Research Centre on the day of recruitment, as well as being returned to the Bristol Centre by pre-paid return addressed envelopes at the end of the trial period. Consent forms faxed to the University of Bristol will be stored on the REDCap system as well as the paper copy being retained in the trial master file.

Parents/legal guardians choosing to complete paper SRQs will be asked to post the completed SRQ to the University of Bristol using a freepost envelope. The data will then be entered into the patient's TRANSFoRm profile, identified by unique study ID, by the research nurse. TRANSFoRm is accessed via a secure website requiring a password. The GP will manually enter the study ID at the point of handing the study information pack to the participant.

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 (REDCap) from the clinical data (TRANSFoRm) and data protection requirements will be further enforced by best practice trial management procedures.

12.5 Data backup systems

TRANSFoRm: The data stored in TRANSFoRm will be backed up every 12 hours, using a bash script, encrypting and copying outside the server, within the KCL secure server environment.

University of Bristol: University of Bristol servers are backed up in accordance with University policies. 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.

12.6 Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections - in line with participant consent.

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised, individual patient data will be made available for secondary research,

conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose. Access to patient identifiers would be subject to confirmation that the secondary research protocol has been approved by a UK Research Ethics Committee (REC) or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

A summary of the overall trial results will be made available to those parents/legal guardians who have confirmed that they wish to receive them.

13. QUALITATIVE ASSESSMENT

13.1 Recruitment/sampling

Purposive sampling will select participants in order to capture maximum variation in views and experiences of a range of parents/legal guardians and clinicians. During the internal pilot, a TRANSFoRm platform prompt will remind clinicians to advise parents/legal guardians about the interviews. From parents/legal guardians that agree to trial participation and the interview, a purposive sample will be drawn in relation to site, arm of the trial, and socio-demographic variables such as ethnicity, socio-economic status. Parents/legal guardians who decline trial participation will also be invited to be interviewed and from those that agree, a purposive sample will be drawn in relation to primary care site and socio-demographic variables. At the point of decline, parents/legal guardians will be asked by the GP if they are interested in participating in a qualitative interview about their reasons for declining. The GP will provide interested parents/legal guardians with a short information sheet and take the parent/ legal guardian's contact details to email or fax to the study team. Clinicians, e.g. GPs and Nurse Practitioners, will also be purposively sampled in relation to site and length of time since qualification. Sample sizes will be determined by data saturation, such that no new themes are emerging from the data by the end of data collection.[57] We anticipate including up to 20 clinicians, 20 participant parent/ legal guardian interviews and 15 parent/legal guardian decliner/withdrawal telephone interviews will be sufficient to achieve this aim.

In-depth interviews will be conducted with participating parents/legal guardians (from all arms of the trial) at least 14 days after randomisation by telephone. Interviews with parents/legal guardians who declined to participate will be conducted around seven days of declining by telephone. Clinician interviews will be conducted towards the end of the internal pilot and trial and will also be conducted by telephone. Consent of participants will be taken verbally on the phone and audio-recorded.

A flexible topic guide will be devised to ensure that the primary issues are covered across all interviews, but it will incorporate considerable flexibility to enable participants to introduce unanticipated issues, and they will be modified to reflect findings as they emerge. 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. Clinician interviews are expected to last around 30 minutes, parent/legal guardian interviews 40-60 minutes and those with parents/legal guardians who decline trial participation 10-20 minutes. With informed consent, interviews will be recorded using a digital voice recorder, transcribed and anonymised to protect confidentiality.

13.2 Analysis

Interview transcripts will be checked for accuracy and then imported into NVIVO qualitative data analysis software. Analysis will begin shortly after data collection starts and will be ongoing and iterative – informing further data collection and identifying changes needed to the topic guide. Thematic analysis[58], utilising a data-driven inductive approach, will be used to identify and analyse patterns and themes of particular salience for participants and across the dataset using constant comparison techniques[59 60].

Transcripts will be read several times, to gain familiarisation with the data and initial ideas noted. The transcripts will then be examined on a line-by-line basis with inductive codes being assigned to the segments of the data that provide insight into the participants' views and understanding of their experiences. An initial coding frame will be developed and new data will be compared initially 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 incorporating themes within other themes[59 60] and the coding frame will be modified, if needed, as analysis develops. The data will be scrutinised for negative cases and reasons for the deviation will be explored by comparison with the whole dataset.

Transcripts from the parents/legal guardians' interviews and the clinician 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 team (CC and JH); any discrepancies will be discussed within the team and resolved to achieve coding consensus and maximal rigour.

14. MONITORING, AUDIT AND INSPECTION

REST will be conducted in line with appropriate legislation (including EU/UK clinical trial regulations and Health and Safety regulations), ICH GCP and the UK Policy framework for Health and Social Care Research. The trial will be reviewed by a NHS REC as part of the new Health Research Authority (HRA) approval process.

The study will be monitored and audited in accordance with the University of Bristol policy, which is consistent with UK Policy Framework for Health and Social Care Research and the MHRA Regulations 2004. All study related documents will be made available on request for monitoring and audit by the sponsor, the relevant REC and for inspection by the MHRA or other licensing bodies. Any monitoring of the trial will be carried out by UHBristol under a SLA.

14.1 Monitoring plan

A risk-based 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 UHBristol in line with the SLA.

The plan will be implemented by the trial team and overseen by University Hospitals Bristol NHS Foundation Trust (UHBristol), 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].

14.2.1 Before the trial

Where necessary the Centre Principle Investigators (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 collaborating centres (Southampton) in order to document preparedness to conduct recruitment locally.

14.2.2 After the start of recruitment

- 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%;
- 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 Research and Innovation (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.

14.2.3 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 eCRFs/CRFs have been filled out correctly;
- directly access source documents for comparison of data therein with the data in the eCRFs/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.

14.2 Protocol deviations

Any protocol violations will be investigated, reported and assessed in relation to patient safety and data integrity by the study team, and escalated if required, to the independent monitoring team at UHBristol, who will oversee the monitoring of the trial on behalf of the trial sponsor. There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately.

14.3 Direct access to source data / documents

The Centre PIs and trial sites will allow monitors (from UHBristol 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 PIS.

14.4 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 will also be conducted in accordance with all applicable regulatory requirements including but not limited to:

- MHRA Regulations 2004, as amended in 2006 and any subsequent amendments
- EU Directive 2001/20 EC
- UK Policy Framework for Health and Social Care Research
- Declaration of Helsinki (1996)
- Medicinal Products for Paediatric Use

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

15.2 Ethical and safety issues

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. 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 (DBS) checks. REST will be conducted in line with appropriate legislation (including EU / UK clinical trial regulations and Health and Safety regulations), International Conference on Harmonisation Good Clinical practice (ICH GCP) and the UK Policy Framework for Health and Social Care Research. The trial will be reviewed by a NHS REC as part of the new HRA approval process.

REST clinicians will be asked to prescribe ciprofloxacin 0.3% ophthalmic solution off-label as per usual clinical practice. We do not anticipate this being an issue for the MHRA as it is not unusual for a study (particularly in children) to use medicines that are within current NHS use, off-label. Once MHRA approval is secured, the University of Bristol's trial insurance policy will provide REST clinicians with no-fault compensation for trial use of the ciprofloxacin drops.

15.3 REC and MHRA review and reports

This protocol and related documents will be submitted for review to a UK REC and MHRA for Clinical Trial Authorisation (CTA).

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 DMEC and TSC as appropriate.

DSUR 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 National Institute for Health Research (NIHR), the Sponsor, the REC and the MHRA within one year of the end of the trials.

Trial summary results will be uploaded to The European Medicines Agency Clinical Trials Database (EudraCT) within 6 months of the end of the trial and the upload will be confirmed to the MHRA via CT.submission@MHRA.gov.uk

15.4 Public and Patient Involvement

During recruitment, PPI meetings will focus on troubleshooting and advising on site/parent/legal guardian newsletters to aid recruitment. At the end of the study, PPI meetings will focus on interpreting results and dissemination methods - PPI members will help identify non-academic dissemination avenues, and will advise on materials for press releases, print media, social media and parent/legal guardian and patients facing materials, including presentation of results using a parent/legal guardian/child-friendly animation. Our PPI participants will be supported by our PPI coordinator and offered research training via FutureLearn online and People in Health, West of England (see http://www.phwe.org.uk/). The TMG will use plain language and provide a glossary of terms and acronyms.

15.5 Investigators responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required, have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the eCRFs/CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved the REC that they receive and ensure that the changes are complied with.

15.6 Indemnity

The University has arranged “No Fault” (non-negligent harm) insurance to provide compensation to research participants, if on the balance of probabilities, they suffer bodily injury, death, disease, illness or disability (including exacerbation of an existing condition) caused by the administration to or use by them of any drug involved in the trial or directly due to participation in the Clinical Trial.

15.7 Amendments

The Sponsor will determine whether an amendment is substantial or non-substantial. Protocol amendments will be submitted to the REC and MHRA, on the agreement of the Sponsor and with the prior approval of the funder. Amendments will also be notified to NHS R&D departments of participating sites to confirm ongoing capacity and capability to deliver the study.

16. DISSEMIINATION POLICY

16.1 Dissemination policy

Once analyses are complete, but prior to publication, we will discuss results with as many of our stakeholders as possible, in order to include all perspectives regarding the implications of our results. Current stakeholders include: parents/legal guardians, primary care clinicians, NICE, the MHRA, NHS England, RCGP, The Royal College of Paediatrics and Child Health (RCPCH), Primary Care CCGs, Walk-in Centres, Out of Hours Centres, NHS 111, general practices, and Acute Trusts. In addition to the final monograph for the NIHR HTA Programme, we will publish the 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 an international audience. This will include presentations at meetings and bespoke written executive (and 'actionable') summaries for UK based stakeholder groups, service users and international paediatric associations.

In addition to the academic and clinical outputs, we will work with our PPI contributors to identify avenues to disseminate findings to parents/legal guardians and the public. Together with the PPI contributors, the PPI coordinator and the Centre for Academic Primary Care (University of Bristol) (CAPC) communications officer, we will create parent/legal guardian-facing materials, write print media releases, utilise social media.

Assuming we demonstrate clinical non-inferiority at no (or minimal) additional cost, the beneficiaries of this new knowledge is likely to include: (i) children and parents/legal guardians; (ii) their contacts; (iii) the NHS. The adoption of either topical or delayed antibiotic treatment for AOMd would quickly result in fewer children exposed to systemic antibiotics, which would lead to reduced incidence of antibiotic side effects (most commonly diarrhoea, vomiting and skin rashes) and reduced selective pressure on antimicrobial resistance.

Children are key transmitters of both antibiotic susceptible and resistant bacteria. We anticipate antimicrobial resistance effects being reduced by topical compared to oral antibiotic use, and in trials of delayed prescribing, antibiotic use is reduced by up to 60%, again reducing exposure of a substantial population of children to antibiotics. Infections caused by antimicrobial resistant microbes result in longer illnesses and higher NHS costs.

Children carrying fewer antimicrobial resistant microbes are less likely to transmit these to their families, e.g. vulnerable grandparents, and wider community contacts, e.g. day care and nursery. Reducing the selective pressure on antimicrobial resistance could lead to reduced NHS costs in the longer term as well as fewer primary care contacts for advice regarding systemic antibiotic side-effects.

Our PPI work indicates tolerance in some parents/legal guardians for mild ongoing symptoms, suggesting that even if one or both new treatments fail to reach the pre-specified equivalence margin,

we will still be able to provide valuable information to inform prescribing. Some parents/legal guardians may be keen to avoid systemic antibiotics because of worries about side-effects or resistance or might find the use of drops more convenient. Therefore, Information about the relative effectiveness of drops or delayed prescribing may still result in changes in the use of antibiotics.

16.2 Intellectual property (IP), authorship eligibility guidelines and any intended use of professional writers

Imperial College London (ICL) and Kings College London (KCL) are part of a formal partnership, which owns the TRANSFoRm software that will be used within this project. The software is available open-source upon condition of acknowledgement. The project will acknowledge the TRANSFoRm software and European collaboration, which developed and owns the TRANSFoRm IP.

Specifically, for REST the TRANSFoRm software will be used for the following:

- recruitment pop-up reminders in EHR – the system monitors selected codes via the API;
- collection of anonymised information on non-consented and excluded subjects;
- record of consent;
- randomisation;
- clinical outcomes pre-populated from EHR;
- PROMs on web, mobile devices delivered according to the study timetable;
- embedding of a study specific code in the EHR data extraction for post-entry routine data;
- provenance trace for resolution of data queries and GCP compliance;
- data extraction into any CDISC compliant study data management system;
- study “workbench”. This enables real time monitoring of sites and of data completeness by the study centre.

We intend to implement the foreground IP through:

- an update to NICE guidance;
- a guide for Medicine Management Teams within commissioning organisations detailing how to incorporate findings into local formularies;
- engaging clinical networks.

Apart from this, the project does not rely on any specific background owned by the applicants apart from the highly relevant and significant expertise and experience of the team, which is outlined in this application.

Any foreground IP relating to the TRANSFoRm software will rest with the owners of the background (KCL and ICL).

NHS Bristol CCG will lead on the management of all other IP generated. A collaboration agreement has been created prior to the start of the award in which NHS Bristol CCG will be formalised as leading on IP management and will licence the IP to the other collaborators for non-commercial and teaching purposes.

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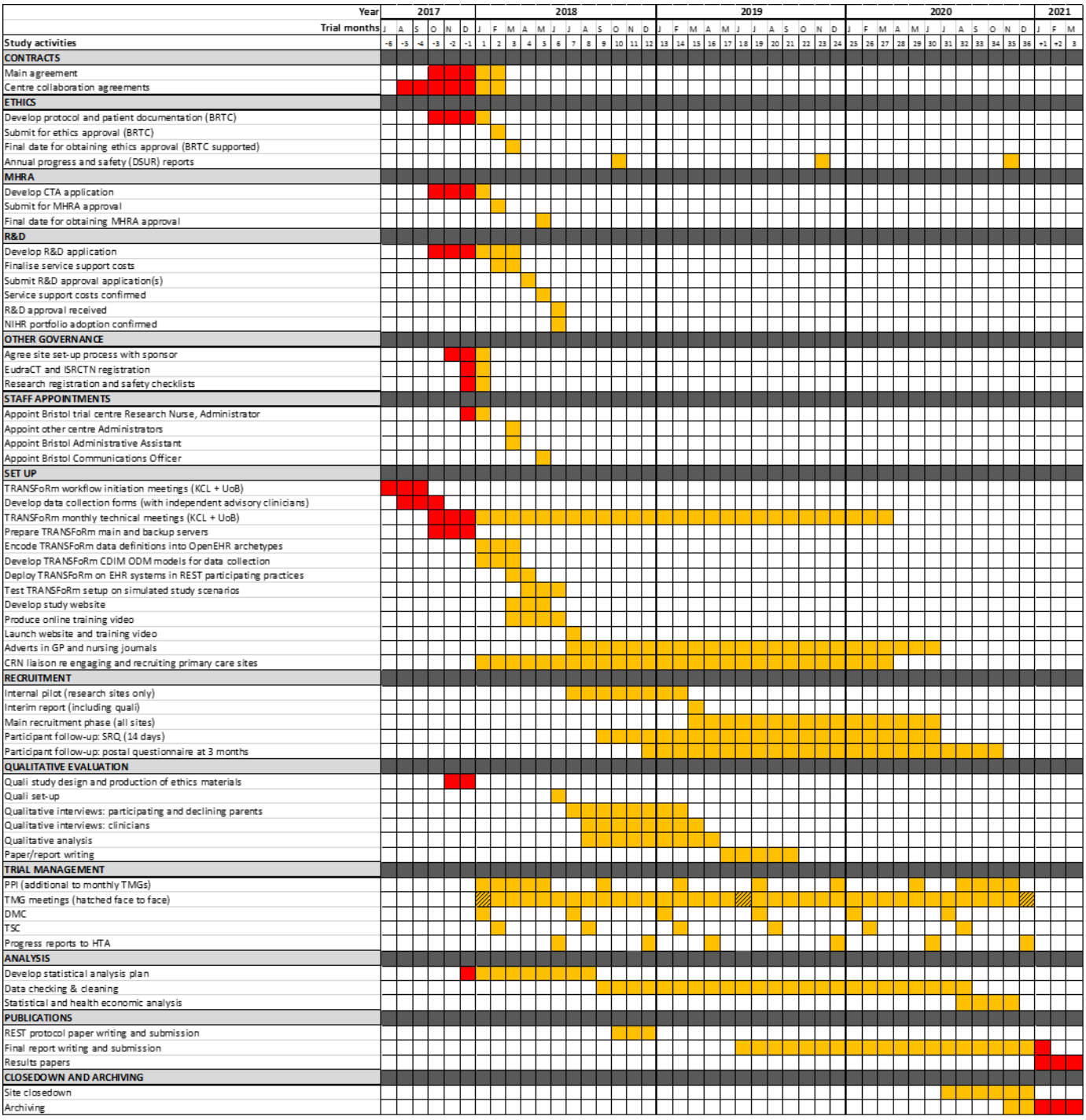
18. APPENDICES

Appendix 1: Gantt chart and key milestones



Appendix 2: Medicines for Children: Ciprofloxacin Drops for Infection

Medicines for Children information for parents and carers

Ciprofloxacin drops for infection

This leaflet is about the use of ciprofloxacin drops to treat infections of the outer ear that are caused by bacteria (sometimes called bacterial otitis externa). They are not suitable for ear infections caused by viruses.

This leaflet has been written for parents and carers about how to use this medicine in children. Our information sometimes differs from that provided by the manufacturers, because their information is usually aimed at adult patients. Please read this leaflet carefully. Keep it somewhere safe so that you can read it again.

Ciprofloxacin drops are often used for the eye, but it is safe to be used in the ears as well. If you are concerned, talk to your doctor, nurse or pharmacist.

Name of drug

Ciprofloxacin drops (sip-roh-flox-ass-in)
Common brand: Ciloxan®

Why is it important for my child to take this medicine?

Ciprofloxacin is an antibiotic. By giving it regularly in the way that your doctor has told you to, it should kill the bacteria causing the infection.

What are ciprofloxacin drops available as?

- **Ciprofloxacin 0.3% drops** (supplied in a 5 mL dropper bottle)

When should I give ciprofloxacin drops?

Ciprofloxacin drops are usually given **two or three times** each day. Your doctor will tell you how often to give the drops to your child.

- **Twice a day:** give the drops once in the morning and once in the evening. Ideally, these times are 10–12 hours apart, for example some time between 7 and 8 am, and between 7 and 8 pm.
- **Three times a day:** give the drops once in the morning, once in the early afternoon (e.g. straight after school) and once in the evening. Space these times out as evenly as possible.

Give the drops at about the same times each day.

How much should I give?

Your doctor will work out the number of drops (the dose) that is right for *your* child. The dose will be shown on the medicine label.

It is important that you follow your doctor's instructions about how much to give.

How should I give the drops?

- Wash your hands thoroughly with soap and hot water.
- Shake the bottle.
- Your child needs to have their head tilted to one side. (They could rest their head on a pillow.)
- Put the tip of the dropper just inside the ear hole. Try to avoid touching the nozzle on to the ear. Gently squeeze the drop(s) into the ear.
- Your child should keep their head tilted to one side for a minute or so.
- Wipe the nozzle with a clean tissue after each use.

Repeat the above steps for the other ear if necessary.

When should the medicine start working?

The drops will start to work straight away but it may take 2–3 days before your child starts to feel better. It is important that you give the whole course of drops that your doctor has prescribed, even when your child feels better. This is to make sure that all the bacteria are killed and the infection doesn't come back.

What if my child is sick (vomits)?

You do not need to worry if your child is sick, as the drops will still work.

What if I forget to give it?

If you usually give it twice a day

If you remember up to 4 hours after you should have given a dose, give your child the missed dose. For example, if you usually give a dose at about 7 am, you can give the missed dose at any time up to 11 am. If you remember after that time, do not give the missed dose. Just give the next dose as usual.

If you usually give it three times a day

Do not give the missed dose. Just give the next dose as usual.

What if I give too much?

It is unlikely that you will cause any harm if you give your child extra drops by mistake. If you are worried that you may have given your child too much, contact your doctor or local NHS services (111 in England and Scotland; 0845 4647 in Wales). Have the medicine or packaging with you if you telephone for advice.

Are there any possible side-effects?

We use medicines to make our children better, but sometimes they have other effects that we don't want (side-effects).

Side-effects you must do something about

If your child is short of breath or is wheezing, or their face, lips or tongue start to swell, or they develop a rash, they may be allergic to ciprofloxacin. Take your child to hospital or call an ambulance **straight away**.

Important things to know about taking antibiotics

- It is important that your child completes the course of antibiotic. This means that they must take the medicine for the number of days that the doctor has told you to, or until all of the medicine has been taken. If you stop giving the antibiotic too soon, the bacteria that are left will start to multiply again, and may cause another infection. There is also a risk that these bacteria will be 'resistant' to the first antibiotic. This means that it might not work next time, and your child might need a different antibiotic, which might not work as well or cause more side-effects.
- Try to give the medicine at about the same times each day, to help you remember, and to make sure that there is the right amount of medicine in your child's body to kill the bacteria.
- Only give this medicine to your child for their current infection.
- Never save medicine for future illnesses. Give old or unused antibiotics to your pharmacist to dispose of.
- Only give the antibiotic to the child for whom it was prescribed. Never give it to anyone else, even if their condition appears to be the same, as this could do harm.

⚠ If you think someone else may have taken the medicine by accident, contact your doctor for advice.

- Antibiotics only kill bacteria; they do not kill viruses. This means that they do not work against colds, sore throats, flu or other infections that are caused by viruses. Your doctor will not prescribe antibiotics for these illnesses.

Other side-effects you need to know about

- Your child may develop a rash or itching in the ear(s) while using the drops. This will stop when the course of treatment is finished. If it is a problem, contact your doctor for advice.

There may, sometimes, be other side-effects that are not listed above. If you notice anything unusual and are concerned, contact your doctor. You can report any suspected side-effects to a UK safety scheme at http://www.mhra.gov.uk/yellowcard.
More information on side-effects can be found in the following leaflet http://www.medicinesforchildren.org.uk/side-effects-childrens-medicines.

Can other medicines be given at the same time as ciprofloxacin drops?

- You can give your child medicines that contain paracetamol or ibuprofen, unless your doctor has told you not to.
- Check with your doctor or pharmacist before giving any other medicines to your child. This includes herbal or complementary medicines. However, most medicines can be given safely while using ciprofloxacin drops.

Is there anything else I need to know about ciprofloxacin drops?

- Do not put cotton wool (or anything else) into the ears during the course of treatment.
- Ciprofloxacin is widely available in the UK in other formulations, including as eye drops. Ciprofloxacin eye drops (Ciloxan 0.3%) are the most commonly used preparation in the UK for ear infection. It is safe for ciprofloxacin eye drops to be used in the ears as well. If you are concerned, talk to your doctor, nurse or pharmacist.
- Once opened, ciprofloxacin drops should not be kept for longer than 4 weeks.

Where should I keep this medicine?

- Keep the drops in a cupboard, away from heat and direct sunlight. They do not need to be kept in the fridge.
- Make sure that children cannot see or reach the medicine.
- Keep the medicine in the container it came in.

Who to contact for more information

Your doctor or pharmacist will be able to give you more information about ciprofloxacin drops and other treatments for ear infection.
You can also get useful information from:

England
NHS 111: 111 - www.nhs.uk

Scotland
NHS 24: 111 - www.nhs24.com

Wales/Galw Lechyd Cymru
NHS Direct: 0845 4647 - www.nhsdirect.wales.nhs.uk

Northern Ireland
NI Direct: www.nidirect.gov.uk

www.medicinesforchildren.org.uk

RCPCH Royal College of Paediatrics and Child Health
WellChild the national charity for sick children
NPPG Neonatal & Paediatric Pharmacists Group
Health & care information you can trust