Results, lessons learned and recommendations from the REST randomised controlled trial of antibiotic strategies for children with acute otitis media with discharge

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LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| AMR | Antimicrobial resistance |
| AOM | Acute otitis media |
| AOMd | Acute otitis media with discharge  |
| API | Application Programming Interface |
| BNF | British National Formulary |
| BRTC | Bristol Randomised Trials Collaboration |
| CAB | Change Advisory Board |
| CCG | Clinical Commissioning Group |
| CDIM | Clinical data information model |
| CDISC | Collaborative Data Standards Interchange Consortium |
| CHMP | Human medicines committee |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case report form |
| CRN | Clinical Research Network (funded by NIHR) |
| CTDMS | Clinical Trial Data Management System |
| CTIMP | Clinical trial of an investigational medicinal product |
| CV | Curriculum vitae |
| DH&SC | Department of Health and Social Care |
| DNC | Data node connector |
| eCRF | Electronic case report form |
| EAM | External auditory meatus |
| EDC | Electronic data capture form |
| EHR | Electronic health record, provided by companies such as EMIS® and TPP SystmOne® |
| EMA | European Medicines Agency |
| ENT | Ear nose and throat (surgical specialism) |
| EoI | Expression of Interest |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GUI | Graphical User Interface |
| IHE | Integrating the Healthcare Enterprise |
| IQR | Interquartile range |
| IT | Information technology |
| ITT | Intention to Treat |
| LHS | Learning health system |
| NHS | National Health Service |
| NHIS | Nottinghamshire Health Informatics Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| ODM | Operational data model |
| OMQ | Otitis Media Quality of life questionnaire |
| OTC | Over the counter |
| PI | Principal investigator |
| PIS | Patient information sheet |
| PP | Per protocol |
| PPI | Patient and public involvement |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PREAR  | Painful Runny EAR (first iteration of REST) |
| PROMs | Patient Reported Outcome Measures |
| RCGP | Royal College of General Practitioners |
| RCT | Randomised controlled trial |
| REST | Runny Eat STudy |
| RFD | Retrieve Form for Data Capture |
| RISP | Research information sheet for practices |
| RPE | Retrieve Process for Execution |
| SDM | Study Data Model |
| SRQ | Symptom and Recovery Questionnaire |
| TMG | Trial Management Group |
| TRANSFoRm | Translational Research and Patient Safety in Europe (name of electronic trial platform) |
| TSC | Trial Steering Committee  |
| TSS | Study System |

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ABSTRACT

Background

Acute otitis media (AOM) is a painful infection of the middle ear commonly seen in children. In some children, the ear drum spontaneously bursts, discharging visible pus (otorrhoea) into the outer ear (AOMd).

Objective

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 AOMd.

Design

Pragmatic, three arm, individually randomised (stratified <2 vs. ≥2 years), non-inferiority, open trial with economic and qualitative evaluations, supported by a health-record-integrated electronic trial platform (TRANSFoRm) with internal pilot.

Setting

44 English GP practices

Participants

Children aged ≥12 months and <16 years whose parents (carers) were seeking medical care for unilateral otorrhoea (ear discharge) following recent (≤7 days) onset AOM.

Interventions

Interventions: (i) immediate ciprofloxacin (0.3%) solution, four drops three times daily for seven days; or (ii) delayed ‘dose-by-age’ amoxicillin suspension three times daily (clarithromycin twice daily if penicillin allergic) for seven days, with structured delaying advice. All parents given standardised information regarding symptom management (paracetamol /ibuprofen/ fluids) and to complete the course.

Comparator

Immediate ‘dose-by-age’ oral amoxicillin three times (clarithromycin twice) daily for seven days. Parents received standardised symptom management advice along with advice to complete the course.

Main outcome measure

Time from randomisation to the first day on which all symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea, and episodes of distress/crying) were rated ‘no’ or ‘very slight’ problem (without need for analgesia).

Methods

Participants recruited from routine primary care appointments. Planned sample size 399 children. Follow up using parent completed, validated symptom diary.

Results

Delays in software deployment and configuration led to low recruitment and trial closure at the end of the internal pilot. Twenty-two children (median age 5 years; 62% boys) were randomised: five, seven and ten respectively to immediate oral, delayed oral and immediate topical antibiotics. All received prescriptions as randomised. Seven (33%) fully adhered to treatment as allocated.

Symptom duration data were available for 17 (77%) children. The respective median (IQR) number of days until symptom resolution in the immediate oral, delayed oral, and immediate topical antibiotic arms were 6 (4, 9), 4 (3, 7), and 4 (3, 6). Comparative analyses not conducted due to low numbers.

There were no serious adverse events, and six reports of new or worsening symptoms.

Qualitative clinician interviews showed the trial question was important. When the platform functioned it was liked and worked as intended. However, staff reported malfunctioning software for long periods resulting in missed recruitment opportunities. Troubleshooting the software placed significant burdens on staff.

Limitations

The overriding weakness was the failure to recruit enough children.

Conclusions and future work

We were unable to answer the main research question due to a failure to reach the required sample size. Our experience of running an electronic platform supported trial in primary care has highlighted challenges from which we have drawn recommendations for the NIHR and the research community. These should be considered before such a platform is used again.

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SCIENTIFIC SUMMARY

Background

Clinical

Acute otitis media (AOM) is a painful infection of the middle ear commonly seen in children. Sometimes the ear drum spontaneously bursts, discharging (AOMd) visible pus into the outer ear. Current evidence suggests most children with AOMd are treated with ‘immediate’ (to be started the same or next day) oral antibiotics.

However, there is uncertainty regarding whether oral antibiotics could be delayed (‘wait and see with a standby prescription’) or immediate topical (ear drop) antibiotics could be as effective. Both options offer the advantage of reducing exposure to systemic antibiotics, reducing the risks of side effects and reducing the selective pressure systemic antibiotics place on antimicrobial resistance.

Electronic trial platform supported recruitment

A review of AOM incidence suggested the average GP practice manages 76 children with AOM per annum, of which around 15% have AOMd, equating to 11 AOMd presentations per annum. Our sample size requirement (399 children) necessitated working with 175 GP practices, recruiting over two winters and one summer. We determined that an electronic trial platform prompting and supporting recruitment would be necessary to maintain trial activity over this number of sites.

Objectives

The main objective was 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 AOMd.

Secondary objectives were:

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 satisfaction with treatment; and adverse events
3. To compare hearing loss and AOM/AOMd recurrence rates at 3 months
4. To understand parent and clinician views of AOMd trial participation, adherence and satisfaction with allocated treatment
5. To evaluate the relative antimicrobial resistance impact of immediate topical, delayed oral and immediate oral antibiotics.

Methods

Design

Pragmatic, three arm, individually randomised (stratified <2 vs. ≥2 years), non-inferiority, open label trial with economic and qualitative evaluations, with participant identification and data collection supported by ‘TRANSFoRm’, an electronic trial platform integrated into the electronic health record system.

Patient eligibility

Children whose parents or legal guardians (from here on ‘parents’) were seeking primary medical care for unilateral otorrhoea as the presenting symptom of acute (≤7 days) AOM.

#### Included

* Age ≥12 months to <16 years
* Presenting with recent onset (≤7 days) unilateral AOM with recent onset (≤7 days) otorrhoea, currently visible or seen by parent within the last 24 hours
* Attending with parent legally able to give consent
* Parent willing and able to administer eardrops
* Parent willing, able and available to complete the daily symptom and recovery questionnaire and receive regular telephone calls from the study team.

Excluded

* Symptoms or signs suggestive of bilateral AOM or AOMd
* Symptoms or signs suggestive of serious illness and/ or complications e.g. mastoiditis and/ or requires immediate hospitalisation
* Requiring immediate oral antibiotics
* Child at high risk of serious complications due to significant immunosuppression; heart, lung, renal, liver or neuromuscular disease co-morbidities; Trisomy 21; cystic fibrosis; or craniofacial malformation such as cleft palate.
* Grommet tube *in situ* in the otorrhoea ear
* Currently on oral or topical antibiotics
* Allergy to ciprofloxacin
* Allergy to penicillin (or anaphylaxis to another beta lactam agent) *and* allergy to the suggested alternative, clarithromycin
* Child taken part in any research involving medicines within the last 90 days
* Child already participated in REST.

Randomisation and concealment

Following eligibility confirmation and consent, concealed randomisation, stratified by age (<2 years and ≥2 years) was conducted using TRANSFoRm.

Interventions

#### Intervention 1

Immediate ciprofloxacin (0.3%) ear drop solution, four drops given three times a day for 7 days, with an advice sheet on how to administer the ear drops, the importance of completing the course and symptom management.

#### Intervention 2

Delayed dose-by-age oral amoxicillin suspension given three times a day (clarithromycin if penicillin-allergic or other suitable oral antibiotic as chosen by the GP) for 7 days, and an advice sheet with standard, structured delaying advice, the importance of completing the course and symptom management.

#### Comparator

Immediate dose-by-age oral amoxicillin (clarithromycin if penicillin-allergic or other suitable oral antibiotic as chosen by the GP) given three times a day for 7 days, and an advice sheet with information regarding the importance of completing the course and symptom management.

Outcomes

#### Primary outcome

Time to resolution of all pain, fever, being unwell, sleep disturbance, otorrhoea, and episodes of distress/crying rated ‘no’ or ‘very slight’ problem by parents without need for analgesia, using a validated self-report scale known to be sensitive to change. Parents were asked to complete the symptom and recovery questionnaire in the evening of each day as a record of the child’s overall experience during the previous 24 hours.

#### Secondary outcomes

* Duration of ‘moderately bad or worse’ symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea; episodes of distress/crying)
* Adverse events, defined as new or worsening symptoms including diarrhoea, rash, and vomiting
* Serious adverse events, defined as death, hospitalisation or new/ worsening disability
* Parent satisfaction with treatment at day 14
* Treatment adherence and analgesic use up to symptom resolution
* NHS resource use and costs for 14 days
* Antimicrobial resistance in stool samples

Sample size

Our previous trial comparing immediate oral with delayed oral antibiotics showed children with AOMd (combined immediate and delayed strategy) took a median of 3 days to achieve the REST primary outcome. Our patient PPI group advised the maximum difference they regarded as unimportant was 1.25 days. With 20% loss to follow-up and 90% power to establish the above the non-inferiority margin, 399 children (133 per arm) were necessary at the 1.25% (two-comparison adjusted) significance level.

Qualitative interviews

Since recruitment was significantly slower than expected, qualitative interviews focused on understanding the views and experiences of staff using TRANSFoRm. Staff were purposively sampled in relation to site, role and whether the practice successfully recruited patients. In depth interviews were conducted using a flexible topic guide, audio recorded and transcribed. Data were analysed thematically.

PPI

Extensive PPI was undertaken during the development of the protocol and study materials. Members inputted into the development of the primary outcome and identified the most significant symptoms that should be used to judge recovery as: pain; fever; being unwell; sleep disturbance; otorrhoea; and episodes of distress. The PPI group commented on the symptom recovery questionnaire and patient facing materials. Our PPI contributor helped determine trial strategy following a European Medicines Agency report on the safety of fluoroquinolone antibiotics.

Results

Electronic trial platform

Delays in setup and functionality of TRANSFoRm led to critically low recruitment and early trial closure. Key challenges included: (i) under-estimating the technical challenge of integrating platform and electronic health record (EHR) software; (ii) under-estimating the resources required to troubleshoot resulting problems; (iii) the need for repeated site platform reinstallations which was time consuming, as it needed to be installed on individual workstations; (iv) multiple and complex site IT security arrangements, often involving third parties without contracts covering research; (v) failure to include a platform ‘dashboard’ function resulting in the TMG being unaware when the platform was/was not functional; and (vi) progressively reduced site staff motivation to re-install and use the software. That said, and acknowledging it was ‘too little too late’, when the electronic trial platform was operational, clinicians reported strongly liking its features and that it assisted recruitment as intended.

Trial

The first site opened on 5th April 2019 and the trial was closed on 31st March 2020, due primarily to critically low recruitment but secondarily to the onset of the 2019/2020 SARS-CoV-2 pandemic. At study closure, 122 GP practices from 12 CRNs had expressed an interest, of which 71 confirmed participation, 61 received sponsorship, 44 opened to recruitment with TRANSFoRm installed on 72 clinical computers, and seven sites randomised 22 children.

Children were 62% boys with median age 5 years. Five, seven and ten were respectively randomised to immediate oral, delayed oral and immediate topical antibiotics. All received prescriptions as randomised. Seven (33%) parents fully adhered to treatment as allocated.

Symptom duration, parent satisfaction and resource use data were available for 17 (77%) children. The primary outcome of median symptom duration was 4 ((interquartile range) IQR 3, 7) days for the whole group, respectively the median (IQR) number of days to symptom resolution in the immediate oral, delayed oral, and immediate topical antibiotic arms were 6 (4, 9), 4 (3, 7), and 4 (3, 6). Formal comparative analysis was not conducted due to low numbers. There were six reports of new or worsening symptoms. There were no serious adverse events. Eighty-eight percent of parents were either ‘extremely satisfied’ or ‘satisfied’ with treatment. NHS resource use and costs were low.

Qualitative

Sixteen staff were interviewed, including GPs, practice managers, IT leads and research staff. Clinicians felt the trial addressed an important question and wanted a system that automatically captures patient data. When TRANSFoRm functioned it was liked and worked as intended. However, staff reported malfunctioning software for long periods resulting in missed recruitment opportunities. The experience of getting TRANSFoRm to work was frustrating and time consuming, diverting staff from core activities. Staff felt TRANSFoRm was not sufficiently developed for use. Installation was reliant on practice level IT expertise, which varied between practices. Although most had external IT support, this rarely included supported for research IT. Arrangements for approving new software varied across practices and often, but not always, required authorisation from CCGs.

Conclusions

Insufficient participants were recruited to answer the main research question. We were unable to establish the feasibility of running a platform supported pragmatic trial for AOMd in primary care. The late development and intermittent functioning of the TRANSFoRm platform within the SystmOne electronic health record system resulted in low recruitment and failure to reach the required sample size. Our experience has highlighted the technical issues which need to be overcome before electronic trial platform technology should be adopted in the primary care setting.

We have carefully documented our experience and provided recommendations (reproduced below) for those conducting the following activities: site identification; site training; platform development; platform installation and platform function monitoring. Addressing these challenges will be necessary if the UK is to lead the world in the delivery of pragmatic research that quickly and efficiently produces generalisable new knowledge to improve patient care.

Recommendations

The main research question remains unanswered. These recommendations focus on potential improvements to aid study management in the primary care setting and implementation of an effective electronic trial platform These are grouped by those responsible for the following activities: site identification; site set up; site training; platform development; platform installation; troubleshooting; platform function monitoring and data management. Finally, there are two recommendations for national stakeholders, including DH&SC and NIHR.

The NIHR CRN

1. *CRNs should keep logs of which sites have been invited, when and how many times. These should be shared with study teams, in order to populate Consolidated Standards of Reporting Trials (CONSORT) flow diagrams and allow a description of the generalisability of the recruiting sites.*

Sponsors

1. *Sponsors should consider accepting electronic versions of delegation logs with e-signatures. These should be designed such that submission of incomplete logs/ CVs is not possible.*
2. *With large distributed trials with many sites a robust electronic data management system to track documentation should be employed.*

Trial management teams

1. *Where online site training is used, studies should provide training via a website that provides automated reminders and notifies the Sponsor and study team when training is complete.*

Electronic study platform

#### Developers

1. *Use of electronic trial platforms should be used to harness the unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where the key ‘drop offs’ are in the recruitment process from presentation to consent.*
2. *All necessary platform preparatory activities and required resources should be clearly defined, taking care not to under-estimate either.*
3. *The skills needed to set up a trial platform, and to set up a trial are distinct and complementary. Ideally teams should be co-located to ensure platform specifications meet individual trial requirements.*
4. *Platform software needs to be compatible with all practice software systems.*
5. *Closer integration with EHR providers would prevent incompatible updates [NB. this could be obviated if national criteria were agreed or the trial platform was integral to the EHR].*

#### Installers

1. *Project teams need to work closely with EHR providers and CCGs from the study outset to agree the software deployment process and the validation criteria required [NB. this could be obviated if national criteria were agreed or the trial platform was integral to the EHR].*
2. *A pilot install incapable of being used for recruitment and therefore not a site agreement requirement) should be performed on one computer in each practice, tested, and left to run for a week, before installing software on to other machines.*
3. *Where software re-installation is required, it must be done in a way which does not disrupt the work of the practice.*

#### Troubleshooters

1. *Electronic study platforms require teams dedicated to: (i) development; and (ii) troubleshooting.*
2. *Careful consideration should be given to who is responsible for troubleshooting – while it may seem obvious this is done by the trial team (since it involves interacting with sites), it requires awareness of platform function and may therefore be better provided by the platform development team.*

#### Function monitors

1. *Electronic trial platforms would be best served by a dashboard function to monitor and log platform functionality in real-time, providing real-time alerts and diagnostics for reduced function, and logging functionality across time and space.*

#### Data managers

1. *The format of the final dataset to be extracted from the study database should be pre-specified to ensure appropriate data format and avoid the submission of linked clinical and personal data.*

National stakeholders, including DH&SC and NIHR

1. *Research funders need to formally recognise the potential of electronic study platforms if they wish to put the NHS at the leading edge of pragmatic research globally, allowing the delivery of new, near-real-time generalisable knowledge, and providing unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where the key ‘drop offs’ are in the recruitment process from presentation to consent, that influence final study sample representativeness.*
2. *The NIHR and research funders should consider convening a meeting of national stakeholders to define a strategy for the development, implementation, and ongoing management of electronic study platform software.*

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PLAIN ENGLISH SUMMARY

Ear infections are common in childhood. Some are complicated by a burst eardrum followed by ear discharge. The usual treatment for this is a short course of antibiotics taken by mouth. However alternative treatments with antibiotic drops, or by using ‘a wait and see’ policy before starting antibiotics, would result in taking less antibiotic use and reduce the subsequent risk of antibiotic resistance which is bad for patients and the environment.

This study set out to see if these alternative treatments were as effective as the usual treatment for children with discharging ears.

Although ear infections are common, only one in six children develop an ear discharge, so only a few children might be available to take part at each GP practice. We planned to use an electronic recruitment system to help get us enough patients. The system (called ‘TRANSFoRm’) was designed to remind busy GPs and nurses about the study and take them step by step through the recruitment process as well as support trial processes.

Although TRANSFoRm had been developed and tested, it had not been used in the GP practices before. We were surprised to find there were many technical problems in setting up TRANSFoRm in GP practices. And staff were too busy, and/or did not have enough skills to overcome the technical issues. As a result, recruiting patients was slow and the study was halted before we had enough children to answer the main research question. In total we managed to get 44 GP practices and twenty-two children, but this was not enough.

We still think that this kind of research and electronic trial platforms are important. We have noted many system and technical issues which need to solved to enable funders and researchers to use this recruitment approach in the future.

**Word count:** 296/300

# INTRODUCTION

## Funding history

Through its research prioritisation process, the NIHR HTA determined the need for evidence to improve the management of AOMd. This resulted in the publication of two commissioning briefs.

We responded to the first brief (See HTA commissioning brief 15/32) in 2015 where we specified a two-arm trial and in which the stated research question was: ‘What is the clinical and cost effectiveness of topical antibiotics as compared to oral antibiotics in children with acute otitis media presenting with acute ear discharge?’ and was called the Painful Runny EAR (PREAR) study. The Stage 1 proposal was shortlisted to Stage 2 but was not supported. In fact, in their 23 December 2015, the Commissioning Board stated it “was unable to commission any proposals in this topic area, which will now be returned to the prioritisation group for possible re-advertisement in the future.”

A further brief was issued in 2016 (See HTA commissioning brief 16/85) with the research question unaltered but now specifying in addition to topical antibiotics two other groups, namely immediate oral, and no or delayed oral antibiotics. The present Runny Ear STudy (REST) was the successful application in response to this second brief. Four changes were made in response to the board concerns over our PREAR proposal:

1. That the two-arm (immediate oral vs. immediate topical antibiotics) was normalising antibiotic use for this condition. We addressed this by the addition of the third "delayed oral antibiotics" arm.
2. That the primary outcome was pain only - and not a broader measure of symptoms. We addressed this by changing the primary outcome to ‘time to resolution of pain, fever, being unwell, disturbed sleep, otorrhoea and episodes of distress’.
3. We amended the conservative recruitment projections based on only 6% of children with acute otitis media having otorrhoea). We have revisited this assumption and, based on recent evidence, we amended this to 15% which we believed was a more realistic estimate; and
4. That the study did not plan to look at antimicrobial resistance in the ear caused by topical treatment or otorrhoea virology. At Expression of Interest we had strengthened these elements, but in response to the Board's November 2016 comment to reduce costs we removed all microbiological elements (since they were not in commissioning brief 16/85).

## Structure of this report

REST suffered from delays in set up followed by slow recruitment. This was the main reason for trial closure, though the trial was actually closed at the COVID-19 pandemic onset which made further recruitment unsafe, since many children were being assessed and managed using remote ‘telephone only’ systems. The study was planned, and hence presented, as a full trial with internal pilot. In the event only the internal pilot data were collected, and we present these results together with the qualitative data from participating site staff and parents. Formal statistical comparisons and economic analyses were not conducted due to the low numbers, but clinical and economic descriptors are presented.

## Clinical background

Acute otitis media (AOM) is a common childhood infection usually presenting with the rapid onset of ear pain. Infection may follow other respiratory tract infection. In young children the infection may present as pulling at the ear, increased crying, and poor sleep. Either bacteria or viruses may be involved. Risk factors include exposure to smoke, use of pacifiers, and daycare attendance. The diagnosis is usually made by examination of the eardrum in those with suggestive symptoms. Signs of AOM include redness or bulging of the tympanic membrane. New ear discharge following an episode of ear pain is also suggestive of the diagnosis.

AOM is important to children, parents and the NHS for three reasons. First, 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.(2, 3) Moreover, children with AOMd have a worse prognosis, and higher rates of parent reported pain (at one week), repeat AOM episodes (at three months), and hearing problems (at three months).(3)

Second, although estimates of parental costs (travel, over the counter (OTC) medicines and lost earnings) vary,(4-6) even the lowest suggests costs of £4M in England and Wales per annum. Also, AOMd results in health service consultations with over 90% of UK parents attending primary care for each episode,(7) 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).(4, 5)

Finally, more children with AOM and AOMd receive an oral antibiotic in the UK(8) and US(9) than for any other respiratory infection, with three-quarters of GPs prescribing oral antibiotics to at least 80%.(10, 11)

There is good evidence that children with AOMd benefit from immediate oral antibiotics. The number needed to treat is three to reduce the proportion of children with pain and/or fever at 3 to 7 days compared with placebo/ no treatment.9 As a result, NICE recommends immediate antibiotics should be considered.21 However, oral antibiotics also cause side effects, are associated with subsequent eczema and hay fever,22 and are associated with population23 and patient24 level antimicrobial resistance. The UK’s Antimicrobial Resistance Action Plan endorses research to preserve antibiotic effects,25 and as described below there are plausible alternative treatment options to immediate antibiotic prescription ‘delayed prescribing’ and antibiotic drops.

### Delayed oral antibiotics

Current evidence for AOMd symptoms is limited to showing: (i) the superiority of immediate antibiotics over placebo/ no treatment;(12) and (ii) the similarity of delayed compared with immediate oral antibiotics in children with AOM.(1) Research into the clinical effectiveness and economic implications of delayed oral antibiotics is needed since a delayed prescription would be likely to reduce exposure of children to antibiotics - around 24% of children with AOM given a delayed prescription in our trial were actually given the antibiotic.(1)

### Immediate topical antibiotics

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 grommets (ventilation/tympanostomy tubes), it has been shown that topical antibiotics can reach the infected middle ear against a stream of discharge,(13) and that compared with oral antibiotics, they are more effective for otorrhoea duration, AOM recurrence and side effects.(13) This study also showed topical antibiotic to be safe8 and cost-effective (from a societal perspective).(14) 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.(15) If 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.

### Reducing systemic antibiotic exposure

Two systematic reviews found no evidence regarding the relative antimicrobial resistance (AMR) impact of topical and systemic antibiotics.(16) (17) 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 sore throat(18) and acute lower respiratory tract infection(19)). Therefore, as with ciprofloxacin drops, we expect delayed antibiotics to result in fewer side effects and reduce antimicrobial resistance impact, and that it too would be recommended for clinical use if symptom relief was non-inferior.

### Summary

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 therefore proposed a three arm RCT to investigate the clinical effectiveness and economic implications of topical or delayed oral 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.

## Rationale for trial design

### Trial efficiency

AOMd is less common than AOM accounting for around 15% of presentations. This means around 15 children (≥12 months to <16 years) can be expected to present with AOMd per annum to larger (≥10,000) GP practices, according to Royal College of General Practitioners (RCGP) data,(20) requiring dozens of sites. Taking a standard approach to the set-up of such a study, utilising face to face training and distribution of recruitment packs would require a huge logistical effort at high cost. Therefore, to maximise trial efficiency and procedure quality, we planned to adopt the following strategies:

1. To focus on larger practices
2. To utilise remote training and induction of trial sites through the use of online trial procedures training
3. To use simplified research governance procedures
4. To train and incentivise receptionist teams to steer eligible children into appropriate appointments
5. To use an embedded electronic trial platform (called TRANSFoRm, see below) to flag participants and to simplify recruitment procedures
6. To use standard FP10 NHS prescriptions in an open design
7. To direct participants to address post randomisation procedural questions to a Research Nurse using a telephone call on day 1.

### Non-inferiority design

There is good evidence showing that immediate oral antibiotics are superior to placebo for reduction of pain/fever in children with AOMd.(2) As a result, NICE recommends immediate oral antibiotics ‘be considered’.(21) Our 2015 audit shows current practice complies with NICE guidance - 88% of children with AOMd were given oral antibiotics (of which 97% were coded as immediate). Since we expect ciprofloxacin 0.3% ear drops (current NHS 5ml cost = £6.01)(22) will have fewer side effects(13) and less impact on antimicrobial resistance than immediate oral antibiotics (100ml amoxicillin 250mg/5ml NHS cost = £1.93),(22) clinical adoption of the new treatment would be recommended if its clinical effectiveness is at least as good as (non-inferior) current standard therapy(23) and if it was 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(24) and acute lower respiratory tract infection(19)). 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.

### Primary outcome

In keeping with previous research,(1, 2, 13, 25, 26) 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. 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 was therefore the time to all of pain, fever, being unwell, sleep disturbance, otorrhoea, and episodes of distress/crying being rated ‘no’ or ‘very slight’ problem by parents without need for analgesia. We used a validated(27) Symptom and Recovery Questionnaire (SRQ), known to be sensitive to change,(1) similar to SRQs we have used our previous studies,(1, 28-30) where we achieved >80% diary completion rates with Research Nurse telephone support. The presence and severity of each symptom was 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’. The intention was for symptoms to be recorded until all symptoms have been rated zero for two consecutive days, or in the event of non resolution for a maximum of 14 days, (research has shown that the symptoms of AOM have resolved in 90% children by day 8).(31) Symptoms were recoded via the TRANSFoRm platform(32) (or using a paper Symptom and Recovery Questionnaire (SRQ)) with real-time monitoring of data completion.

### Secondary outcomes

Secondary outcomes also reflected their importance to parents(25) and the NHS. Those recorded in the first 14 days (on the SRQ) included: time until symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea, episodes of distress/crying, appetite and interference with normal activities) are rated ‘moderately bad or worse’ (score of ≥3 on our validated scale(27)); adverse events (diarrhoea, rash, vomiting and severe complications at days 7 and 14); parent satisfaction with treatment (days 7 and 14); and faecal AMR profile at 2 weeks and 3 months. We measured treatment adherence, treatment crossovers at day 7, and analgesic use to symptom resolution (or day 14, SRQ). Finally, we asked parents to record details of NHS resource use up to day 14 on the SRQ.

Longer term outcomes measured at 3 months (via the TRANSFoRm platform or paper postal questionnaire) included AOM and AOMd recurrence; serious complications (such as mastoiditis) and parent reported hearing loss at 3 months (measured using the OMQ-14(33) questionnaire successfully used in the recent(34) HTA ‘AIRs’ trial). Parents reporting serious complications were to be asked to give permission for the study team to conduct an additional review of their child’s notes.

### Electronic trial platform

#### Previous evidence and experience

Data standards for research data collection have been formulated by the clinical trials community via The Collaborative Data Standards Interchange Consortium (CDISC) over several decades, with an established pathway for data management from source to submission for regulated clinical trials. Using CDISC standards there has been a steady move away from paper case report forms (CRFs) towards electronic data capture (EDC) systems. Given the rapid expansion of the use of electronic health record systems EHRs in clinical settings, it has been proposed that EHRs could be the primary point of data entry for a clinical trial. However, direct collection of data into digital form, referred to as eSource, can only be achieved if the EHR is able to support research quality data collection. Good Clinical Practice (GCP) principles need to be adopted to ensure that the requisite standards are in place for eSource, while changes are made to the data collection process and governing regulations to fit in with this electronic context.(35)

There are three models of eSource currently being explored: (i) entry into a Clinical Trial Data Management System (CTDMS) with transfer to the HER; (ii) entry into a CTDM with copying to both the EHR and the EDC; and (iii) collection within the EHR with transfer to the EDC. Local preferences, maturity of EHR systems and sponsor requirements are likely to maintain this heterogeneous approach, emphasising the paramount importance of adherence to standards. The Integrating the Healthcare Enterprise (IHE) collaboration ([www.ihe.org](http://www.ihe.org/)), has developed a set of profiles for eSource,(36) the Retrieve Form for Data Capture (RFD) and Retrieve Process for Execution (RPE) specify forms and workflow respectively. Several proof-of-concept studies using IHE profiles have been completed. These include, integration of Common Data Elements from NCBI CaBIG EVS into the RFD profile,(37) and STARBRITE, a single site proof of concept implementation within a heart failure clinical trial, without further progress in the field.(38)

Within the academic and pharmaceutical trials world there has been a move to ‘real world’ clinical trials as a means of gathering more data, more quickly on the likely effectiveness of treatments, to satisfy increased regulatory requirements in this area.(39) It is proposed that embedding and integrating research into electronic record systems would enable automation of the some elements of the trial’s screening process with eligibility criteria matched directly with EHR held data.(40). Potential participants matching exclusion criteria need not be flagged. Secondly, for those potentially eligible data held in the her can be used to pre-populate the eligibility form. A similar process can be used to pre-fill electronic case report forms (eCRFs). In a reverse process trial data can be added back to the EHR.(41) The ability to place trial information in routine EHRs, at the point of collection, would be a significant step towards safer and more efficient clinical trials.(42)

Real world trials have not yet progressed to using eSource by default, still requiring a large investment in data collection and validation.(43) Closing this step would go a long way to providing an end-to-end ‘research and learning’ continuum for a learning health system (LHS), where research and knowledge translation are routinely transacted via IT systems. Use of robust data standards, such as the CDISC suite, when interacting with EHRs are essential to the operation of the LHS in order to overcome the ‘silo of excellence’ culture prominent in healthcare research, and lower the barrier to entry for traditional clinical environments.(35) (44)

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).(45) Advantages include: (i) increased data accuracy, including anonymised recording of the characteristics of eligible patients declining participation, thereby providing a greater understanding of final sample representativeness; (ii) reductions in data management; (iii) increased safety, by ensuring trial data is within the clinical record; (iv) easier and therefore more efficient trial monitoring; (vi) EHR management of trial workflow, prompts and alerts for recruitment and follow up, and patient reported outcomes;(46) and (vii) the use of Clinical Data Interchange Standards Consortium (CDISC) standards for data capture.(47)

#### Within REST

Within-consultation ‘hot’ recruitment of patients with incident conditions is significantly more challenging than ‘cold’ recruitment of patients with prevalent conditions, who can be contacted electronically or by letter.36 The extra workload and time needed both to set up and to recruit within a normal consultation are major barriers to participation by GPs and practices.36

Participation can be increased where there is perceived clinical value and / or benefit to patients, adequate remuneration for time and streamlined recruitment processes that minimize workload.(48) One approach to overcoming these barriers is through use of a trial platform.

The REST study was designed to collect quantitative data using the TRANSFoRm clinical trial platform, originally developed as part of the EU FP7 funded TRANSFoRm Programme.(32) TRANSFoRm is designed to integrate with primary care EHR electronic medical records, 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 recorded by parents via the web and smartphones (iOS and Android). The system was fully GCP validated as part of a European trial on Gastro-oesophageal reflux diseases, and registered with EudraCT (number 2014-001314-25).

The basic components of the system are: (i) a Study System (TSS) that manages projects, sites and workflow; (ii) middleware that managers authentication and messaging; (iii) a system for triggering and storing PROMs; (iv) Data Node Connectors (DNC), specific to each EHR system, that link 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 were developed, specifying the data elements to be captured, and their linkage to the TRANSFoRm Clinical data Information Model (CDIM), structured according the CDISC Operational data Model (ODM), and the timeline according to the CDISC Study Data Model (SDM). Further ODM files containing questions for the PROMS were developed in combination with structured searches for data elements that were pre-populated by the data in the EHR.

Two areas of the added value of the TRANSFoRm system specific to REST were: (i) the triggering of ‘real time’ eligibility reminders when potential recruits were being seen by clinicians; and (ii) streamlined study processes after identification, with access to REST study specific documentation, prepopulated consent forms and ‘real-time’ randomisation.

### Trial intervention selection

#### Oral antibiotics

For the oral (immediate and delayed) we wanted to reflect routine care and appropriate bacteriological cover. A 2010 study of 256 children with AOM recruited from primary care(3) showed 84% of the 38 children with AOMd received an immediate prescription for amoxicillin with a further 5% receiving oral erythromycin, 3% topical gentamicin and 8% receiving no antibiotic. In the majority of children (22/38 (58%)) a recognised bacterial pathogen was isolated. : *Streptococcus pneumoniae* (n = 5), *Group A Streptococcus A* (n=7), *Staphylococcus aureus* (n=7), *Pseudomonas* (n = 2) and *Haemophilus influenzae* (n= 3).(3) A study of 177 children with AOMd isolated single pathogens 70 (39%) samples, whereas 2, 3, and 4 bacteria were detected in 54 (30%), 20 (11%), and 7 (4%) cases, respectively.(49) Nontypeable *Haemophilus influenzae* was the most common and was identified in 90 children (51%), followed by *Moraxella catarrhalis* (35%) and *Streptococcus pneumoniae* (27%).(49) Children with coinfections, including nontypeable H. influenzae, had significantly more frequent recurrent AOM (adjusted odds ratio 6.6, p=0.029).(49)

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. UK primary care practice is to prescribe amoxicillin ‘dose-by-age’. However, we used the latest British National Formulary (BNF) for Children prescribing guidance to prevent under- and overdosing the oldest and youngest children. Clarithromycin is a commonly used, and well tolerated alternative for penicillin allergic children. Hence we selected oral amoxicillin with the option of clarithromycin in the event of recorded penicillin allergy.

#### Topical antibiotics

We considered there were four main advantages in selecting ciprofloxacin 0.3% as the topical antibiotic. First, it has low potential for AMR since blood stream absorption of ear drop quinolones has been shown to be extremely low, measured at no higher than 10ng/mL in one study of children and adults given 0.3% ofloxacin solution,(50) which is less than 1% of the concentration typically seen after oral dosing. We used four drops of 0.3% ciprofloxacin three times daily and expect to see similar low blood levels to those reported for ofloxacin. Typically a drop is about 50µL,(51) giving a total daily dose of 1.8mg. Although we are not aware of any studies measuring respiratory or gastrointestinal tract quinolone exposures following ear use, even if 100% was absorbed and excreted into the gut this would be less than 2mg per day. In contrast, the typical oral dose for a child is 10 mg/kg two or three times daily – equating to 300mg daily for a 10kg one year old. It is not surprising then that evidence suggests the risk of developing AMR post ear drop application in these locations is very low.(52)

Second, ciprofloxacin ophthalmic 0.3% drops are widely available, which is a requirement for this study since recruitment will take place in a large number of primary care sites dispensed by high-street pharmacies in response to standard FP10 NHS prescriptions. It is usual practice in primary and secondary care to use the eye drop formulation for ear treatment, because the ophthalmic formulation is considerably less expensive, and more readily available, than the otic formulation. Prescribing in REST was therefore off-license, and the study Sponsor ensured that the University of Bristol’s no-fault indemnity applied to this form of ciprofloxacin.

Third, the drops are colourless and odourless, so they did not interfere with parental assessment of otorrhoea. Finally, at the concentrations achieved in the middle ear, ciprofloxacin 0.3% drops are active against the most commonly isolated otorrhoea microbes from children presenting to primary care, namely *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae and Pseudomonas aeruginosa*.(3)

We decided against using a topical aminoglycoside, mainly because of the potential for ototoxicity. Topical antibiotics are thought to penetrate from the middle to inner ear via the round window. This results in high local concentrations in the inner ear tissues and potential for ototoxicity. One systematic review in animals reported widespread ototoxicity with topical aminoglycoside antibiotics,(53) and the ototoxic properties of aminoglycosides have been intentionally used to ablate vestibular function in humans with severe middle ear disease.(54) There is also a genetic mutation, occurring in around 1% of the population, which predisposes to ototoxicity at low drug exposures.(55) Although the evidence of aminoglycoside ototoxicity is debated in humans, especially at the time of an active infection,(56) and there are other advantages of aminoglycoside preparations (e.g. unlike ciprofloxacin, aminoglycoside-steroid combination preparations are widely available), the British National Formulary states that topical aminoglycosides are contraindicated in patients with a perforation of the eardrum or grommets, and such medico-legal concerns would have significantly reduced willingness of trial clinicians to recruit.

We also decided against an antibiotic-steroid combination drop because although there is evidence that, for children with grommets a topical steroid-antibiotic combination is superior to an oral antibiotic alone in reducing the discharge,(13) and superior to topical antibiotic alone,(57) (58) an industry study has shown that ciprofloxacin alone was more effective than a steroid only preparation,(59) suggesting that while steroids may have additional benefit to antibiotics, antibiotics are an essential ingredient. Some animal studies have shown that an antibiotic-steroid combination slows the healing of perforated tympanic membranes compared with antibiotics alone. (60) (61) While a number of aminoglycoside-steroid containing preparations are available, no combination of steroid with ciprofloxacin was widely available in the UK at the time of trial design, meaning that ciprofloxacin was not only suitable, but the only non-aminoglycoside topical antibiotic option available.

### Economic evaluation

It seemed likely intervention costs and clinical outcomes would be similar across the three groups. However, we proposed to explore costs and outcomes from the NHS perspective because we anticipate fewer side-effects and repeat consultations for delayed and topical antibiotics.

### Potential harms

Since an established treatment (immediate antibiotics) has been demonstrated to provide benefit then to avoid prolonged symptoms of pain in children it is important that we demonstrate that the proposed treatments are non-inferior. In November 2018 the European Medicines Agency’s (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) issued a notification regarding the safety of ciprofloxacin. The EMA’s human medicines committee (CHMP) subsequently endorsed the recommendations of the PRAC and concluded that the marketing authorisation of medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended. The CHMP review concerned only medicines given systemically (by mouth or injection) and inhaled medicines. The use of quinolones was restricted with additional warnings. Since the systemic absorption of 0.3% topical ciprofloxacin is low, in consultation with the TMG PPI member, the TMG did not think this presented any additional risks for REST participants.

## Measuring and mitigating threats to trial validity

### External validity

Our intention was to maximise generalisability by asking clinicians to invite all potentially eligible children to participate. As we have with previous studies,(30, 62) where study invitations are declined, parents were asked if basic details (age, gender and global illness severity) could be recorded via the TRANSFoRm platform.

### Internal validity

#### Randomisation

Concealed randomisation stratified by age (˂2 vs. ≥2 years) was used to ensure treatment groups were similar with respect to both measured and unmeasured potential confounders.

#### Treatment crossover and adherence

In an open label trial, which we considered necessary for REST, there was a possibility that children would 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.(63) Higher levels of adherence than this were achieved in the previous open trial of oral vs. topical antibiotics for children with grommets and ear discharge:(13) 88% and 93% fully adhered to oral and topical antibiotics respectively. Minimising treatment crossover was a key clinician training element and the TRANSFoRm platform minimised crossover by guiding clinicians to issue the ‘correct’ treatment. Finally, treatment adherence was monitored via prescribing at the notes review, and using the SRQ.

#### Performance, measurement and attrition bias

Although participants were not be blinded to treatment allocation, given current treatment equipoise and the fact that all participants will receive active antibiotic treatment, we did not consider parent knowledge of treatment allocation would significantly influence their perception of symptom severity. Members of the TMG and statistical team remained blind to treatment allocation until analyses were completed. REST used outcome measures successfully used in our previous studies, (1, 28, 29) and shown to be valid(27) and sensitive to change.(1, 28, 29) We aimed to achieve a minimum 80% follow up rate, but with online data collection and telephone support from an experienced research nurse, we anticipated achieving closer to 90% for our primary outcome.(1, 28, 29)

## Previous or ongoing similar research

We reviewed the literature and trials registries in December 2016 and found no relevant published, completed or ongoing studies in AOMd (without grommets).(15) However we are collaborating with a Dutch group (one shared applicant (AS) and two collaborators (RD, RV)) who are currently conducting a another RCT (<https://www.trialregister.nl/trial/6535>) to investigate the effect of topical antibiotics in otitis media with discharge. While the non-inferiority design and eligibility criteria are similar, the REST and ZonMw applications are complementary with regards:

1. Primary outcomes – REST used the duration and severity of a broader range of symptoms, the Dutch study is using pain and/or fever at 72 hours
2. The Dutch application uses an ear drop containing two antimicrobial agents and a steroid (hydrocortisonebacitracin-colistin, not available in the UK) - we used an antimicrobial only
3. The Dutch study has two arms (topical vs. immediate oral antibiotics) while we had three
4. The Dutch study will use ‘dose-by-weight’ amoxicillin, we used ‘dose-by-age’.

The collaboration has ensured we harmonised outcome definition so we will be able to conduct meta-analyses, and together, the two studies will strengthen generalisability as there is evidence from other trans-European studies that UK and Dutch patients have different illness spectra.

In summary our trial proposed 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. In addition we proposed to demonstrate using a combination of remote training and integrated trial platform efficient trial delivery which would provide a model for future trials of low frequency but important clinical conditions in primary care.(3)

## Study aim

The main aim was 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 AOMd.(64) The research question was ‘Is either ciprofloxacin 0.3% drops, or delayed oral amoxicillin (clarithromycin if penicillin allergic), non-inferior to current usual care (immediate oral antibiotics) for overall illness duration in children with AOMd presenting to primary care?’.

Secondary objectives(64) were:

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 satisfaction with treatment; and adverse events
3. To compare hearing loss and AOM/AOMd recurrence rates at 3 months
4. To understand parent and clinician views of AOMd trial participation, adherence and satisfaction with allocated treatment and
5. To evaluate the relative antimicrobial resistance impact of immediate topical, delayed oral and immediate oral antibiotics.

# METHODS

Here we describe how the REST trial was conducted, first summarising overall trial design, then describing the intended set up and function of the TRANSFoRm trial platform, and then how the trial itself was conducted. A trial protocol has been published in full.(64)

## Design

The trial was designed (Figure 1) as a pragmatic, three-arm, individually randomised (stratified by age <2 vs. ≥2 years), non-inferiority, open label trial comparing: (i) immediate topical ciprofloxacin 0.3% drops with (ii) delayed oral antibiotics; or (iii) immediate oral antibiotics.

## Ethics

Ethics approval was granted by South Central Oxford B Research Ethics Committee on 22 May 2018 (REC reference 18/SC/0181, IRAS project ID: 229293).

## Site requirement assumptions

It was clear at the design stage that recruitment would be challenging due to (i) the acute nature of AOMd requiring ‘within-consultation’ recruitment; and (ii) the relative infrequency of AOMd.

Our detailed recruitment assumptions were based on 2011 AOM incidence data from the RCGP.(20) These are rigorously collected and up to date (since introduction of the 7 and 13 valent pneumococcal conjugate vaccines), and so reflect the incidence of AOM in primary care at the present time. They suggested the average GP practice (with 7,335 patients)(65) would see 76 AOM presentations in children aged >12 months to ≤16 years per annum. Between 15%(3) and 20%(2) of children with AOM are thought to present with AOMd, due to a spontaneous perforation of the tympanic membrane. Using the lower estimate, the average GP practice will see 11 children with AOMd per annum. We therefore intended to focus site recruitment on larger (≥10,000 patients) and/or research active GP practices. We established there were around 680 research-active sites in the eight CRN and Wales areas with whom REST applicants and collaborators had previously worked, and 1,958 practices with list sizes of ≥10,000 in England, to which we anticipate annual AOMd presentations to increase to 15 per practice PA (or one every 3 to 4 weeks).

Based on this, we used the assumptions summarised in Table 1 to arrive at an estimate of the number of primary care sites needed to recruit the sample. Based on these, and a required sample of 399 children (see Sample size), we estimated the number of primary care sites needed to recruit over two winter and one summer season would be 175.



Figure 1. REST study schema

Therefore, given that each trial site might only see one potentially eligible child every 3 to 4 weeks, and the large number of sites required, we concluded it would not be possible for the trial team to provide sites with in-depth support to ensure recruitment. We considered it necessary to use a ‘light touch’, efficient-design trial method, in which clinicians would be prompted and guided through the recruitment process.

Table 1. Recruitment step assumptions

|  |  |  |
| --- | --- | --- |
| *Recruitment step* | *Proportion assumed to progress*  | *Comment* |
| Presentation to invitation ratio  | 0.2 | Low because even in sites in which clinicians are aware of REST, eligible children will present at inconvenient times |
| Invitation to acceptance ratio | 0.67 | Based on PPI feedback |
| Invitation acceptance to eligibility ratio  | 0.8 |  |
| Eligibility to consent ratio | 0.8 | Some parents may change their minds about trial participation during the recruitment process |
| **Product of the above (presentation to consent)** | **0.08** |  |

We considered the use of an electronic trial platform fully integrated into the electronic medical record would maximise the chances of recruitment success. The key specifications we were aware of at trial outset were that full integration would facilitate:

1. Trial reminder ‘pop-ups’ triggered when clinicians entered relevant diagnostic codes in children
2. Auto-provision of patient information sheet (PIS) and other trial materials for potential participants
3. Auto-population of patient characteristics into trial database, reducing data entry time
4. Within consultation confirmation of eligibility
5. Auto-provision of consent form (to be printed and faxed/ emailed to study team)
6. Within consultation randomisation so clinician could provide necessary treatment (using standard NHS prescription)
7. Auto-provision of links for parents to complete symptom recovery questionnaires
8. Auto-population of electronic health record patient follow up data preventing the need for manual review of patient notes.

## The TRANSFoRm electronic trial platform

### Overall structure

Overall architecture is summarised in Figure 2. The TRANSFoRm Clinical Trial software was initially developed as part of the EU FP7 TRANSFoRm project (2009-2015) and evaluated in a 36-site clinical trial.(32) 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. Eligibility criteria and data to be collected was specified through data elements, using 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 were developed separately.



Figure 2 Schema summarising TRANSFoRm architecture

### REST specific functionality

Detailed specifications were agreed before development began (see Detailed TRANSFoRm technical specification for REST v1.4). In summary, we wanted the system to identify potentially eligible children, and then ‘lead’ the clinician though the recruitment process, providing prompts and reminders throughout. REST specific functionality is shown in Figure 3.

#### Recruitment reminders

The system was intended to respond to clinicians’ use of pre-determined Read diagnostic codes by triggering a reminder ‘pop up’ alerting the clinician that the child might be eligible for REST.

Read and ICD-10 clinical codes describing members of the acute otitis media subclass (Table 2) were added to the TRANSFoRm’s study database. The scope was intentionally broad (sensitive) to maximise the chances of identifying potential participants using the wide ranges of codes used by clinicians. This was followed by application of the (specific) eligibility criteria supplied at the beginning of the (electronic) recruitment process to ensure the patient was suitable for the clinical trial. Specifically, the steps followed were:

1. Identify open consultation
 TRANSFoRm’s DNC, using SystmOne’s API, requested to extract information from the currently opened EHR, if any. If the request was not successful, then no consultation was in process. Otherwise, a consultation was taking place and a summarised view, containing demographic data and clinical codes inserted in the record on the current date, was temporarily stored in a local folder of the DNC. Then, a call to TRANSFoRm’s study system retrieved the given list of Read and ICD-10 clinical codes and the age comparison expression.

2. Match patient age.
The system matched the patient’s age, as extracted from the summarised view, with the comparison expression. If the matching proved unsuccessful, the recruitment workflow stopped.

3. Match clinical codes
A search took place to match clinical codes from both the summarised view and the data obtained from the study database.

4. Identify prior trial entry
The algorithm searched for any trial-related clinical code that may have already been inserted in previous consultations to the same patient. (e.g. Read code *XaN0L::Consented* , inserted into record when Consent form is submitted by user) or declined e.g. Read code *XaaFk::Declined*, inserted into record when Decliners form is submitted by user.

##### 5. Following the sequence 1-4

To confirm open consultation, age match, clinical code match and the absence of trial-related codes exist, then a pop-up is displayed to the user to initiate the recruitment process. At the same time, a trial-related clinical code was inserted into the patient record to denote potentially eligibility to the trial (e.g. Read code *XaaEl::Screened* .

##### 6. Pop up disposal

Disposal of the pop-up reminder window was done by the clinician following Microsoft Windows graphical user interface (GUI) standards, that is, button clicking on the red cross icon located on the top-right corner of the pop-up window. The same action to close the window was taken regardless of the outcome (user declined, consented or did not follow through with the recruitment workflow). This was due to the complexity of having more than one possible workflow path at a time and the non-restriction on which electronic forms must be filled in first.

|  |  |  |
| --- | --- | --- |
| *Clinical term* | *SNOMED CT* | *Read Codes* |
| Acute secretory otitis media | 359609001 | F510. F510z FyuP0 |
| Acute otitis media with effusion | 270490007 | XE2QD |
|  Acute transudative otitis media | 35183001 |  |
| Acute otitis media | 3110003 | X00ip |
| Acute left otitis media | 194288009 | F526. |
| Acute right otitis media | 194289001 | F527. |
| Acute mucoid otitis media | 52353000 | F5102 |
| Acute serous otitis media | 194240006 | F5101 |
| Acute suppurative otitis media | 194281003 | F520. F520z |
| Acute secretory otitis media | 359609001 |  |
| Acute exudative otitis media | 19399000 |  |
| Acute exudative otitis media | 194287004 |  |
| Acute tubotympanic catarrh | 85108007 |  |
| Acute sanguinous otitis media | 77478005 | F5106 |
| Acute necrotizing otitis media | 360595002 |  |
| Acute seromucinous otitis media | 232251007 |  |
| Recurrent acute suppurative otitis media | 232251007 | X00iq |
| Acute suppurative otitis media due to another disease | 194282005 | F5203 |
| Recurrent acute non-suppurative otitis media | 232252000 | X00ir |
| Acute suppurative otitis media without spontaneous rupture of ear drum  | 14948001 | F5200 |
| Infective otitis media | 312218008 | XaDmU |
| Acute suppurative otitis media with spontaneous rupture of ear drum | 86279000 | F5201 |
| Subacute nonsuppurative otitis media | 6965008 |  |
| Acute otitis media with effusion | 270490007 | XE2QD |
| Recurrent acute suppurative otitis media with spontaneous rupture of ear drum | 1082561000119104 |  |
| Acute otitis media of left ear with effusion | 15916831000119102 |  |
| Acute otitis media of right ear with effusion | 1090731000119101 |  |
| Acute persistent otitis media | 84261000119106 |  |

Table 2. Codes used to trigger pop-up recruitment reminder

#### Consenting

TRANSFoRm prompted and facilitated the clinician to print the REST consent form and after the parent signed, indicate consent on the system, initiating the trial’s workflow.

#### CRF completion

Electronic Case Report Forms (eCRFs) were presented to clinicians at appropriate points to complete. These were then automatically enter into the study database. Some information was retrieved direct from the SystmOne® record and used to part-fill the form, which could be amended by the user.Once submitted,confirmation was displayed to the user on the screen and completed forms stored in the study database and the SystmOne® record. For the latter, a link to the local copy of the completed record was added. In order to facilitate subsequent tracking of participant progress, trial-specific codes were added to the record: (i) when a patient has been classified as potentially eligible by the plugin; (ii) after submission of the consent or decliner form; and (iii) on trial completion.

#### Recruitment process data collection

There were two approaches planned to collect process frequency data. The first involved the recording of information relevant to the submission of eCRFs by the user. Recorded data consisted of information on the closed pop-up window (see Table 2) or submitted eCRF (consented or declined eCRF), that is, the identifier of the user interacting with the form, the NHS number of the patient at hand and the current date and time. The data recorded was kept locally in a dedicated folder within the clinician or nurse computer and could only be viewed or shared by them. The NHS number was added as relevant data to consider the possibility of a patient being initially discarded by the clinician as potential candidate but recruited at a later stage by the same or a different user. This approach was in the eventuality unsuccessful as local files stored during the running of the recruitment process were overwritten each time a new upgraded version of the DNC was installed. This issue was due to the architecture of the DNC and the restrictions imposed by NHS computers to allow installation of third-party software such as TRANSFoRm (e.g., only Windows-based admin members could permit installation).

The second approach involved auditing the electronic health record for trial-related clinical codes inserted by TRANSFoRm’s DNC during the recruitment workflow. These clinical codes denote potentially eligible and consented participants as well as patients which declined participation.

In November 2019 we tried to estimate the frequency of pop-up disposal by contacting 12 randomly selected sites (of 38 open to recruitment at the time) to request data on the number of times the TRANSFoRm pop-up has been responded to (closed without action, declined or consented) in the previous six months.

Child with ear discharge presents with parent/legal guardian

Within age range (≥ 12m < 16yrs)

Receptionist gives parent copy of PIS to read in waiting room

NO

YES

STEP 2: Eligibility

Clinician confirms eligibility

Excluded from RCT

***- CROMs***

Get parent’s verbal assent for eligibility screening

Baseline data collection to include parent contact details for follow up

Clinician enters listed diagnostic Read code

TRANSFoRm triggers trial reminder pop-up

“Trigger”

STEP 4:

 CROMs

**If consent is not given the parent will be asked to take part in a decliner interview**

STEP 3: Consent

Clinician takes informed consent (and assent if child is old enough**)**

Clinician does not have time

TRANSFoRm provides study summary and option to print consent form

Child not eligible

Parent collects child's stool sample (secondary outcome at 3 months to assess burden of resistance)

 Parent provides secondary outcome data (duration of ’moderately bad or worse symptoms’; adverse events; satisfaction with treatment; treatment adherence & analgesic use; use of NHS resources) via online/paper symptom questionnaire

TRANSFoRm prompts printing of standardised advice sheets on how to use the drops/delayed/immediate antibiotics, and symptom management

STEP 6: Structured advice

STEP 7: Follow-up

Parent provides primary outcome data (time to resolution of all symptoms) via online/paper symptom questionnaire

Parent completes 3-month hearing-related QoL questionnaire online or on paper

 Site completes

3 month primary care notes

review

Parent collects child's stool sample

(secondary outcome at day 14 to assess burden of resistance)

***- PROMs***

STEP 5: Randomisation

TRANSFoRm randomises according to pre-specified schedule

Immediate oral antibiotics

Delayed oral antibiotics

Immediate topical antibiotics

Figure 3. Flow diagram showing role of TRANSFoRm in recruitment and data collection

## Site recruitment

### Site invitation

TRANSFoRm was initially set up to operate with the SystmOne® EHR system. Had this worked well, we intended to expand TRANSFoRm to also work with the EMIS® system. SystmOne® sites were approached in three ways:

1. Through a RGCP bulletin which was distributed to Clinical Research Networks (CRNs) and sites. Sites would then be able to express an interest directly to the study team or through their CRN.
2. Direct to CRNs who regularly promote current research studies to sites. As per standard procedures, a research information sheet for practices (RISP) was provided for CRNs to distribute to sites
3. At CRN networking events where the study was promoted by members of the study team.

Interested sites completed an Expression of Interest (EoI) that was passed onto the study team, triggering the set-up process. To maximise efficiency and procedural quality, we focussed on larger (>10,000 registered patients), as well as research active practices, though the TRANSFoRm platform intended to make the recruitment process streamlined and quick, so even those sites new to research could take part. The Sponsor’s (University of Bristol) ‘green light’ procedure was implemented to document preparedness to conduct recruitment.

### Site approval

The green light process was intended to be ‘light touch’ from the point of view of the Sponsor, who would not need to see each piece of documentation in order to sign off on a site. Instead, the study team entered the details of all the required documentation received (and confirmation of site staff training) onto a study database, providing a summary to the Sponsor to confirm the documents had been received.

Required paperwork included: (i) Organisation of Information document; a completed Site Agreement (signed by practice manager or PI); Delegation Log; (iii) signed and dated CVs from all members of staff that appeared on the delegation log; (iv) GCP certificate (dated with 5 years) for the PI (though all staff were encouraged to submit a certificate if they had one); and (v) completion of site training (see Site training). It was agreed that eligibility could be confirmed by a Nurse or Nurse Practitioner with a GP principal investigator (PI) oversight, meaning the site delegation log had to include a GP as PI.

Once all required documentation was received and entered onto the REDcap database, a record of received documents was emailed to the Sponsor with a request for the site to be ‘green lighted’ and opened to recruitment.

### Site training

The large number of sites with wide geographic distribution meant that face to face training was not feasible. Online study specific modules were developed and recorded using professional actors and hosted by Health Care and Videos (see section 9 APPENDIX). Modules included: (i) introduction from the joint Chief Investigators; (ii) ‘Recruiter Training’; (iii) ‘Recruiting with TRANSFoRm’; and (iv) ‘Recruitment Quick Reminder’. If a staff member was not GCP trained, they were asked to complete ‘Study-specific GCP and Informed Consent’. If staff member was part of the reception team, they were asked to complete ‘Reception Staff Supporting Recruitment’, and if a staff member was part of the admin team, they were asked to complete ‘Chief Investigators Introduce the REST Study’.

Further detailed training videos were provided to help recruiting clinicians navigate the TRANSFoRM system. These can be found in Appendix 1a.

 Hence, staff completed different training modules depending on their role in the study. The study team looked at staff roles on the delegation log to determine what training modules they should be instructed to complete. Site staff were sent the appropriate links to the training videos via email. The study team could see when these modules had been completed on the study training website. Once the PI had completed their training the site could open, with only those who had completed training were permitted to download the TRANSFoRm software and recruit.

## Patient eligibility

### Participants

Children whose parents were seeking primary medical care for unilateral otorrhoea as the presenting symptom of acute otitis media and observed within the previous 7 days.

### Eligibility criteria

#### Inclusion

* aged ≥12 months to <16 years
* presenting with recent onset (≤7 days) unilateral AOM with recent (≤7 days) onset otorrhoea, currently visible or seen by parent within the last 24 hours
* attending with parent legally able to give consent
* parent willing and able to administer eardrops
* parent willing, able and available to complete the daily symptom and recovery questionnaire and receive regular telephone calls from the study team.

Exclusion

* symptoms or signs suggestive of bilateral AOM or AOMd
* symptoms or signs suggestive of serious illness and/ or complications e.g. mastoiditis and/ or requires immediate hospitalisation
* requires immediate oral antibiotics
* child at high risk of serious complications:
	+ Significant immunosuppression
	+ Heart, lung, renal, liver or neuromuscular disease co-morbidities
	+ Trisomy 21, cystic fibrosis or craniofacial malformation such as cleft palate.
* grommet tube *in situ* in the otorrhoea ear
* currently on oral or topical antibiotics
* allergy to ciprofloxacin
* allergy to penicillin or anaphylaxis to another beta lactam agent and, allergy to clarithromycin
* child had taken part in any research involving medicines within the last 90 days
* child had already participated in this trial.

## Interventions

The trial had two intervention arms and a usual-care comparator arm.

#### Intervention 1

Immediate ciprofloxacin (0.3%) ear drop solution, four drops given three times a day for 7 days, with an advice sheet on how to administer the ear drops and standardised symptom management advice.

#### ***Intervention 2***

Delayed dose-by-age oral amoxicillin suspension given three times a day (clarithromycin twice daily if penicillin-allergic or another suitable oral antibiotic as chosen by the GP) for 7 days, and an advice sheet containing structured delaying advice and standardised symptom management advice.

#### Comparator

Immediate dose-by-age oral amoxicillin (clarithromycin twice daily if penicillin-allergic or other suitable oral antibiotic as chosen by the GP) given three times a day for 7 days, and standardised symptom management advice.

## Outcomes

### Primary outcome

Our primary outcome was 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 without need for analgesia. We used a validated self-report scale known to be sensitive to change with study research nurse telephone support. The presence and severity of each symptom was 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’. We asked parents to complete the daily symptom diary in the evening of each day to cover the previous 24 hours. The intention was for symptoms to be recorded until all symptoms had been rated zero for two consecutive days, or in the event of non resolution for a maximum of 14 days. In reality many parents continued to complete scores after two consecutive days of zero scores. Symptoms were recorded via the TRANSFoRm platform (or paper) with real-time monitoring by our research nurse to ensure data completion.

### Secondary outcomes

Secondary outcomes also reflected their importance to parents and the NHS. Those recorded in the first 14 days Symptom and Recovery Questionnaire (SRQ) included:

1. Duration of ‘moderately bad or worse’ symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea; episodes of distress/crying)
2. Adverse events (diarrhoea, rash, vomiting and severe complications at days 7 and 14)
3. Parent satisfaction with treatment (day 14)
4. Treatment adherence and analgesic use to symptom resolution up to day 14 (SRQ)
5. Details of previous 7 days NHS resource use at day 7 and 14 on the SRQ
6. Analysis of stool sample to assess burden of resistance (day 14 and month 3).

## Sample size (non-inferiority)

Our previous AOM trial compared immediate with delayed antibiotics.(1) 73 children had AOMd and they (combined immediate and delayed strategy) took a median of 3 days (IQR 2,4) to achieve the REST primary outcome. We consulted our PPI group to determine the maximum difference they regarded as unimportant, asking: “If you were happy to take part, even if the drops took a little longer to work, how much longer would be acceptable? Please click all that apply.”

Table 3. REST PPI responses regarding maximum unimportant difference

|  |  |
| --- | --- |
| *Maximum no. of days* | *Frequency of response* |
| 1 | 7 |
| 1.5 | 3 |
| 2 | 4 |

Table 3 shows the mean number of extra days considered acceptable by responders, the mean maximum unimportant difference, was 1.39 (95% CI 1.14 to 1.65). This suggests a difference of 1.5 days could be stretching the limit of acceptability to the average parent in this population. However, half the parents were prepared to put up with more than one extra day of symptoms. We therefore concluded an average difference of 1.25 days is collectively acceptable. This would mean for every 5 children treated with immediate eardrops (or delayed oral antibiotics) instead of immediate oral antibiotics, one fewer would have their symptoms resolved or ‘very mild’ within 3 days.

Applying survival curves to produce an increase in median survival (i.e. an increase in time to symptom resolution) of 1.25 days from a median of 3 days would be equivalent to a difference of 16.8% in the cure rate at 3 days. A two-group non-inferiority trial normally assumes 2.5% one-sided Type I error. With REST being a three-group rather than two-group trial; for a 1.25% Type I error to detect non-inferiority for two comparisons with 90% power, a total sample size of 399 (which allows for 20% attrition) is required. Figure 4 shows how we intended this number to be recruited over two winter and one summer season.



Figure 4. Planned recruitment taking account of seasonality, including internal pilot

## Randomisation and concealment

Following eligibility confirmation and consent, children were randomised, stratified by age (<2 years and ≥2 years since children <2 years have been shown to experience longer illnesses)(2) using the TRANSFoRm eSource platform.(32) Blocks of 12 were used for allocation (4 in each arm), since most practices will recruit one or two patients only. Clinicians were not be able to determine treatment allocation pre-randomisation. The randomisation sequence was generated by the Bristol Randomised Trials Collaboration (BRTC), supplied to the TRANSFoRm team, and allocated to successive participants. A system for checking the correct randomisation allocation was built into the TRANSFoRm platform and treatment allocation was checked in the patient symptom questionnaire.

## Data collection

### Baseline

Eligibility criteria, baseline parent reported symptoms and brief clinical examination findings were recorded using the embedded case report from in the electronic health record, managed by the TRANSFoRm platform.(32) The REST research nurse made contact by telephone on day 1 to address any questions or concerns that the parent may have about the trial, and to ensure that the SRQ was being accessed and could be completed without difficulty via the TRANSFoRm platform. If problems were occurring, a shadow paper SRQ was provided.

### Follow up

#### Days 2 to 14

The SRQ was provided in electronic format (either for web or iOS/Android app) via the TRANSFoRm platform. Parents recorded the daily presence and severity of AOMd symptoms (until cessation of all symptoms without need for analgesia): pain, fever, being unwell, sleep disturbance, otorrhoea, episodes of distress/crying, appetite and interference with normal activities. The primary outcome was collected using SRQ with research nurse telephone call (we have achieved <20% primary outcome attrition using this method in other similar trials).(1, 28-30) Daily presence of adverse events were collected, defined as new, or worsening of existing, symptoms, including otitis externa, rash, fungal ear infections, diarrhoea, rash, vomiting and serious AOM complications. We recorded daily measures of study medicine and analgesic/antipyretic use (SRQ). On day 14, parents were invited to record their satisfaction with the trial treatments.

At days 7 and 14, parents were invited to record any use of healthcare resources in the previous 7 days on the SRQ, including information about primary care contacts, community care, use of 111 and Walk-in centres, and hospital services. The research nurse clarified details such as: reasons for the consultation; who was seen e.g. GP, nurse, health care assistant; the type of consultation e.g. face to face, telephone, home visit; and whether it was in-hours or out-of-hours. At the final day 14 telephone call, the research nurse reminded parents to send a stool sample (specimen pot with research laboratory recommended opaque polythene envelopes and label-compliant MailTuffTM outer envelopes sent to parents at day 7) and about the final questionnaire and stool sample at 3 months. The final questionnaire was intended to be provided in electronic format (either for web or iOS/Android app) via the TRANSFoRm platform, but was completed on paper by post since this part of TRNSFoRm was not ready. Here, parents recorded details of AOM and AOMd recurrence, audiology referrals, use of hospital services, hearing loss (using the OMQ-14)(33) and any serious complications.

## Statistics

Participant flow through the trial is summarised by a CONSORT flow chart. Descriptive summary statistics of clinical and demographic characteristics is presented, both overall and separately by arm, in order to describe the study sample and to ascertain comparability of randomisation groups. Continuous data is presented as either mean and standard deviation, or median and inter-quartile range, dependent on data distribution. Categorical data is presented as frequency counts and percentages.

### Primary analysis

The planned primary analysis was to be carried out under the intention to treat (ITT) principle, analysing participants in the groups to which they were randomised, without the imputation of missing data. The primary analysis of effectiveness examines whether immediate topical or delayed oral antibiotics are non-inferior compared to immediate oral antibiotics for symptom duration in children presenting to primary care with AOMd. Symptom resolution over the 14 days of follow up was planned to be compared between children allocated to immediate oral antibiotics (comparator) and those allocated to each of the other treatment groups using a Cox proportional hazards regression model, adjusted for age (stratification variable). The Cox regression model provides an estimate of the Hazard Ratio (alongside the 95% confidence interval and p-value for the comparison) - this indicates the relative likelihood of symptom resolution in intervention vs. control participants at any given point in time. The appropriateness of the proportional hazards assumption would have been investigated. Kaplan-Meir survival curves were planned to be plotted to depict the probability of symptom resolution over time and the median time to symptom resolution for the three treatment groups. The planned primary analysis was not conducted due to the small number of participants recruited and early study closure.

### Secondary analyses of primary outcome

Previous research has suggested that symptoms of AOM will be resolved in 90% of children by day 8. As such the primary outcome was planned to be additionally analysed using an Accelerated Failure Time (AFT) model, which has previously been recommended for studies of resolution of infectious diseases. The AFT model was to be adjusted for age (as in the primary analysis) and the exponentiated coefficients (alongside the associated 95% CI and p-values for the comparison) from the AFT model would have been reported – an exponentiated regression parameter from an AFT model can be interpreted as the percentage difference in time to symptom resolution between treatment arms.

It was planned that the proportion of participants in the immediate topical and delayed oral antibiotics arms who achieve symptom resolution within 3 days were compared (separately) to those in the immediate oral antibiotics arm. The absolute difference then calculated and reported alongside the associated confidence interval, it would then have been reported whether or not the lower limit of the confidence interval lay within the maximum unimportant difference.(64) The planned secondary analyses of the primary outcome were not conducted due to low recruitment numbers and early study closure.

### Secondary outcomes

The primary analysis model was planned to be repeated but with the outcome of symptom resolution being defined as when all symptoms are rated as being “normal/none”, “very slight problem” or “slight problem” (compared to the primary outcome of symptom resolution being defined as all symptoms being rated as “normal/none” or “very slight problem”).

Binary secondary outcomes (e.g. recurrence of AOMd) were to be analysed using logistic regression analysis while semi-continuous scores such as parental/carer satisfaction and hearing loss at 3 months were to be analysed using ordinary linear regression where these variables conformed reasonably closely to a Normal distribution: otherwise negative binomial regression analysis or other suitable alternatives would have been chosen.

### Sensitivity analyses

The primary analysis and AFT models were planned to be repeated with additional adjustment for any prognostic variables demonstrating a marked imbalance at baseline (ascertained using descriptive statistics).

The primary analysis model was to be repeated under the per-protocol (PP) principle – analysis restricted to only those participants deemed to have no major protocol violations.

The sensitivity of the primary analysis to the impact of missing data was planned to be explored by imputing missing primary outcome data and repeating the primary analysis model using the imputed data. The imputation model would include all variables that were part of the ITT primary analysis, baseline and post-randomisation variables associated with missingness and/or prognostic of outcome.

### Exploratory analyses

It was planned to explore potential treatment moderators by including treatment group by moderator variable interaction terms into the primary analysis model (individually).

## Health economics

The objective of the primary economic evaluation was to 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 was to take the form of a simple comparison of NHS costs and outcomes over a period of two weeks from randomisation.

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

### Measurement and valuation of relevant resource use

The resource use for the primary economic evaluation was collected through the SRQ. At day 7 and 14, information in relation to the child’s ear problem was collected on primary care consultations (GP and practice nurse), NHS111 contacts and secondary care service use (Accident and Emergency Attendances, outpatient appointments and inpatient stays). The three-month secondary care resource use was collected through a case note review of the GP practice records. The two sources of data were compared to ensure secondary care data was not double counted.

All resources were valued using unit costs (2018-19 values) from established sources. Primary and community care was valued using Unit Costs of Health and Social Care,(66) NHS Reference Costs for hospital care(67) and the BNfC for prescribed medication.(22)

### Missing data

If the questionnaire had been answered but an individual question had not been completed it was assumed that no health care resources had been used.

### Analysis

The economic analyses were conducted under an ITT approach, i.e. analysing patients in the arm they were randomised, irrespective of any post-randomisation changes. As the follow-up period was less than one year, costs were not discounted.

The cost of each item of resource used during the 2 weeks for primary analysis and from week 2 to 3 months for secondary analysis of follow-up was evaluated as the resource use multiplied by its unit cost. The total cost for each individual patient was calculated as the sum of the cost of resource use items. The mean resource use and costs were estimated and presented by trial arm for each resource use category at 2 weeks and from week 2 to 3 months.

A cost consequence analysis was planned but because of low numbers was not conducted in which the costs to the NHS of the three treatments at 14 days post-randomisation would have been compared with the primary clinical outcome.

## Qualitative

The objective of the qualitative study was to understand the views and experiences of parents and primary care practice staff (including clinician recruiters) of the TRANSFoRm trial in order to inform recruitment strategies for this and future similar trials. Qualitative findings would 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.

### Sampling

Parents who consented to the trial were contacted by phone and asked if they would take part in a qualitative interview. Since there were limited numbers of recruits, instead of taking a purposive approach to sampling, all parents were approached in order to maximize the number of parent views obtained. Parents who declined trial participation and who consented to a qualitative interview were also contacted by text/phone and asked to take part in a short qualitative interview. A sequenced procedure was used to contact potential interviewees. Initial contact was by text so they knew who was calling and the number they were calling from.  If possible the interview time was arranged by text but if there was no response to text then they were called around 3 times at different times of day & on different days of week (respecting their indicated preference for call time).  If there was no response after 3 calls it was assumed this constituted a withdrawal of consent and no further contact was made.

Primary care staff involved in trial processes were invited to take part in qualitative interviews. Staff were purposively sampled to capture experiences of staff with different roles (recruiting clinicians, research and IT support staff) and working at different sites (recruiting, not recruiting or withdrawn).

Sample size was informed by the concept of ‘information power’,(68) with analysis and sampling conducted in parallel and continuous assessment of the suitability of the information within the sample with regard to study objectives. The narrow focus of the study aim on experiences of the trial, the specificity of the experiences and case-based analysis all indicate that higher information power would be possible from a relatively smaller sample.(68)

### Data collection

Semi-structured interviews(69) were conducted with participating parents (from all arms of the trial). Most interviews were conducted with 14 days of recruitment, but a couple were conducted 6 weeks after recruitment (due to reduced availability over Christmas holidays). Interviews with parents who declined to participate were conducted within 3 days of declining. Interviews were conducted by telephone. Parents were contacted by phone, either with a call or a text, and asked to identify a suitable time for the interview, sometimes this was immediately and sometimes it was arranged for a later date.

Interviews with primary care staff were conducted after varied periods of involvement in the trial to capture those with experience of trial processes. Recruiting clinicians were interviewed after they had recruited at least one participant. Primary care staff who had been involved in setting up the TRANSFoRm software were interviewed up to 9 months after their first involvement in the trial.

Flexible topic guides were devised for the parent and staff interviews to ensure that the primary issues were covered across all interviews while allowing considerable flexibility to enable participants to introduce unanticipated issues. The researcher used open-ended questioning techniques to elicit participants’ experiences and views of key events and participants were asked to provide examples. Primary care professional’s interviews lasted up to 45 minutes, parent interviews up to 30 minutes and parent decliner interviews up to 10 minutes. Interviews were recorded using a digital voice recorder, transcribed and anonymised to protect confidentiality.

### Data analysis

Interview transcripts were imported into NVIVO 12 qualitative data analysis software. Analysis began shortly after data collection started and was ongoing and iterative. Thematic analysis,(70) utilising a data-driven inductive approach, was used to identify and analyse patterns and themes of particular salience for participants and across the dataset.(70) The researcher (CC) used line-by-line coding to construct draft coding frames, each based on three transcripts. A combination of deductive coding, based on the aims of the study and the topic guide, and inductive coding, identifying themes within the data, was used. A subset of transcripts were independently coded by members of the team (CC and JH) and data interpretation was discussed to achieve coding consensus and maximal rigour. The coding frame was then modified and applied to the rest of the dataset, with regular meetings with JH to discuss emerging findings. Finally, CC drafted a narrative based on the analysis, with input from JH. Final themes were discussed by the inter-disciplinary Emergent analysis was discussed in multidisciplinary TMG meetings to ensure that findings were trustworthy and credible.

## PPI methods

Extensive PPI was undertaken during the development of the protocol and study materials. Our PPI members inputted into the development of the primary outcome and identified the most significant symptoms that should be used to judge recovery as pain, fever, being unwell, sleep disturbance, otorrhoea, and episodes of distress. The PPI group reviewed the symptom recovery questionnaire and patient facing material and commented on its suitability for use in the study. During recruitment, our PPI contributor advised on the findings of a report published by the European Medicines agency on the safety of fluoroquinolone and quinolone drops.

# RESULTS

This chapter summarises recruitment of sites and participants, and describes the baseline characteristics and outcomes for the 22 children recruited.

## Site recruitment

The first site opened on 5th April 2019 and the trial was closed on 31st March 2020, due primarily to critically low recruitment but secondarily to the onset of the 2019/2020 SARS-CoV-2 pandemic. At study closure, 122 GP practices from 12 CRNs had expressed an interest, of which 71 confirmed participation, 61 received sponsorship, 44 opened to recruitment with TRANSFoRm installed on 72 clinical computers, and seven sites randomised 22 children.

The trial was originally planned to open for recruitment to the internal pilot in time for winter 2018/2019, and then continue recruiting until for another summer and winter until April 2020. Figure 5 shows delays to TRANSFoRm development meant the first participant was not recruited until March 2019, 12 months later than originally planned. New internal pilot dates (June 2019 to December 2019) were agreed with the NIHR HTA in May 2019, but recruitment remained lower than expected, primarily due to poor TRANSFoRm function, and the repeated need to reinstall platform software.

NB. x-axis is non-linear



Figure 5. Participant recruitment against TRANSFoRm activities and delays

## Description of GP recruitment experience

Dr Claire Hombersley of Swanage Medical Centre wrote:

‘Recruiting for REST was relatively straightforward once the software was downloaded and working well. I identified a suitable child [*from*] the sit and wait surgery from the triage details on the appointment screen from our reception staff. They were all aware we were recruiting for a “runny ear” trial and the waiting room had information posters displayed.

‘I was able to see all the children presenting with runny ears when I was working on the sit and wait surgery. If they were suitable and interested in taking part, then I added the otitis media code to the computer that launched the TRANSFoRm platform. The system then presented the required forms in an easy step wise manner starting with the patient information leaflet for the parent and/or patient to read. I then filled in the forms on the system and printed the consent forms. The system uploaded the filled in forms to the primary care record. The PIL and the consent forms were scanned by staff later on. The trial also provided an envelope for the patient containing data protection information, the symptom and recovery questionnaire and freepost envelope, the obligatory free pen and stickers and a further parent information booklet.

‘The system would randomise the patient and then provide the required medication advise sheet to print off for the patient. You followed the A-J Transform forms and then you knew everything was completed and uploaded automatically to the patient record. There was no file containing lots of bits of paper the sort through, it was streamlined and clinician friendly.

‘The first patient I did was time consuming as several of the documents to print out didn’t work. But the next four were quick and I could see the potential in the system. Unfortunately, the runny ears dried up and we did not see another suitable recruit for 12months.’

## Participant recruitment and follow up

30 children/parents were invited to participate of whom 22 agreed, were consented and randomised (Figure 6). Of the eight declining, seven parents stated they did not want their child to participate (no further reason was given) and two were interviewed. No further descriptors for declining children were available with which to assess the generalisability of the final sample.

Five children were randomised to immediate oral antibiotics (control group), ten to topical antibiotics and seven to delayed oral antibiotics. Parents of 17 (77%) children provided primary and secondary symptom outcomes, four (18%) provided stool samples at 14 days, 11 (50%) provided OMQ-14(33) quality of life data (planned at 3 months with four providing this at 2 months due to early trial closure). Primary care medical record notes reviews were conducted manually by site staff in 21 (95%), again four conducted at 2 months early due to early trial closure). Planned stool collection at 3 months was abandoned due to early trial closure.

## Recruitment reminder pop-up

TRANSFoRM included a ‘pop-up’ triggered by the use of AOMd relevant diagnostic codes entered by recruiting clinicians. In November 2019 we randomly selected 12 sites (of 38 open to recruitment at the time) to request data on the number of times the TRANSFoRm pop-up has been responded to (closed without action, declined or consented) in the previous six months. All 12 sites provided data. Table 4 shows that the pop-ups were triggered 11 times at six of the sites, with one participant recruitment linked to these occurrences.

Table 4. Frequency of TRANSFoRm pop-up disposal

|  |  |
| --- | --- |
| *Site name* | *Comment*  |
| Priory Gardens Surgery | 3 pt. pop ups closed |
| Elmwood Family Doctors | 2pt. pop up closed |
| Glendale Surgery | 2pt. pop up closed |
| Well Close Medical Group | 2pt. pop up closed |
| The Westbank Practice | 1 pt. pop up closed |
| Woodlands Family Practice | 1 pt. pop up closed |
| Bradford-on-Avon and Melksham Health Partnership | No pop-ups closed |
| St. Augustine's Medical Practice | No pop-ups closed |
| Chew Medical Practice | No pop-ups closed |
| Medwyn Surgery | No pop-ups closed |
| Eden Court Medical Practice | No pop-ups closed |
| Gillingham Medical Centre | No pop-ups closed |

 

Figure 6. CONSORT flow diagram

## Final sample characteristics and outcomes

### Data completeness

Data were missing for the baseline characteristics of one child (Table 5) while symptom duration data at day 14 were available for 17 (77%) and ear-related quality of life .

Table 5. Data completeness

|  |  |
| --- | --- |
| *Time point* | *N (%)* |
| Randomised | 22 (100%) |
| Baseline data | 21 (95%) |
| Primary outcome | 17 (77%) |
| Symptom data at day 14 | 17 (77%) |
| Resource use data at day 14 | 17 (77%) |
| Stool sample at day 14 | 4 (18%) |
| 3-month data collection | 11 (50%) |

### Baseline characteristics

Of the 22 participants recruited 13 (62%) were male, the median age of the sample was 5 years (IQR 2 to 7), and on a scale of 0 to 10 (where 0=not at all unwell, and 10=extremely unwell) the clinician median rating of how unwell the child is was 2 (IQR 1, 4,) (Table 6). Approximately half of participants had a history of AOM and one third had a history of AOMd. No comment is made regarding potential differences in participant characteristics by treatment arm due to the small numbers recruited.

### Contamination

All antibiotics prescribed at baseline were according to protocol, that is all were one of either oral amoxicillin, oral clarithromycin or topical ciprofloxacin (Table 6) None of the children randomised to receive topical antibiotics were prescribed oral antibiotics, and vice versa, none of the children randomised to receive oral antibiotics were prescribed topical antibiotics. Of the seven children randomised to delayed oral antibiotics six received a prescription at baseline. There was not a recorded prescription for the seventh, which is compatible with how delayed prescribing can be operationalised.(71)

Table 6. Baseline characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | *Immediate oral antibiotics**(n=5)* | *Delayed oral antibiotics**(n=7)* | *Immediate topical antibiotics**(n=10)a* | *Pooled across arms**(n=22)b* |
| *Collected at baseline appointment* |
| Age (years, IQR) | 6 (2, 7) | 5 (3, 11) | 5 (2, 6) | 5 (2, 7) |
| Sex*Male**Female* | 5 (100%)0 | 5 (71%)2 (29%) | 4 (40%)6 (60%) | 14 (64%)8 (36%) |
| Days of discharge (IQR) | 4 (1, 7) | 1 (1, 3) | 2 (1, 3) | 2 (1, 4) |
| Clinician rating of how unwell is child (0=not at all to 10=extremely) | 3 (1, 3) | 1 (1, 4) | 2 (2, 4) | 2 (1, 4) |
| Temperature (°C) | 36.6 (36.6, 36.6) | 36.7 (36.6, 37.0) | 37.2 (36.6, 37.3) | 36.7 (36.6, 37.2) |
| Visible aural discharge:*Yes**No* | 3 (60%)2 (40%) | 6 (86%)1 (14%) | 9 (100%)0 | 18 (86%)3 (14%) |
| Visible perforation:*Yes**No* | 05 (100%) | 07 (100%) | 1 (11%)8 (89%) | 1 (5%)20 (95%) |
| History of AOM (ever):*Yes**No* | 4 (80%)1 (20%) | 4 (57%)3 (43%) | 5 (56%)4 (44%) | 11 (52%)10 (48%) |
| History of AOMd (ever):*Yes**No* | 3 (60%)2 (40%) | 1 (14%)6 (86%) | 3 (33%)6 (67%) | 7 (33%)14 (67%) |
| History of glue ear (ever):*Yes**No* | 2 (40%)3 (60%) | 07 (100%) | 09 (100%) | 2 (10%)19 (90%) |
| *Antibiotic prescription (collected at primary care medical notes review)* |
| Oral amoxicillin  | 5 | 5 | 0 | 10 |
| Oral clarithromycin | 0 | 1 | 0 | 1 |
| Ciprofloxacin drops | 0 | 0 | 10 | 10 |
| No prescription recorded | 0 | 1 | 0 | 1 |
| *Collected from Symptom Recovery Questionnaire at day 1*  |
|  | (n=4) | (n=6) | (n=7) | (n=17) |
| Ever had grommets:*Yes**No* | 04 (100%) | 06 (100%) | 07 (100%) | 017 (100%) |
| Ever had ENT surgery:*Yes**No* | 04 (100%) | 1 (17%)5 (83%) | 07 (100%) | 1 (6%)16 (94%) |
| Ever had eczema, hay fever and/ or asthma:*Yes**No* | 1 (25%)3 (75%) | 4 (67%)2 (33%) | 1 (14%)6 (85%) | 6 (35%)11 (65%) |
| Household smoker:*Yes**No* | 1 (25%)3 (75%) | 2 (33%)4 (67%) | 1 (14%)6 (85%) | 4 (24%)13 (76%) |
| Level of educational qualification (parent):*Left school before 16**Usual age 15/16 exams**Usual age 17/18 exams**Further but not HEI**University degree**Not applicable* | 01 (25%)2 (50%)01 (25%)0 | 1 (17%)1 (17%)02 (33%)2 (33%)0 | 01 (14%)05 (71%)1 (14%)0 | 1 (6%)3 (18%)2 (12%)7 (41%)4 (24%)0 |

a n=9 for other variables other than age and sex

b n=21 for other variables other than age and sex

## Outcomes

### Primary outcome

Symptom duration was defined as the first day on which all symptoms were rated ‘normal, no or very slight problem’, with data available for 17 (77% of those randomised) children. Overall median number of days to symptom resolution was 4 (IQR 3, 7), and the median (IQR) number of days until symptom resolution in the immediate oral, delayed oral, and immediate topical antibiotic arms were 6 (4, 9), 4 (3, 7), and 4 (3, 6) respectively (Table 7). No formal between arm comparative analysis was conducted due to the low numbers recruited.

### Secondary outcomes (first 14 days)

#### Symptom duration

Forty-one percent of parents reported children’s as ‘normal/none or very slight problem’ by day 3 and 65% reported symptoms as ‘normal/none, very slight problem, or slight problem’ by the same time point. The median duration of symptoms for children in all groups rated as ‘normal/none, very slight problem, or slight problem’ was 3 days (IQR 2, 4;(Table 7). For the same outcome, the median number of days in the immediate oral, delayed oral, and immediate topical antibiotics were 3 (3, 4), 4 (2, 6), and 3 (2, 5) respectively. The duration of moderate or worse symptoms are reported by symptom in Table 6.

#### Satisfaction with treatment

While numbers are too low for definitive comment, 88% of parents were either ‘extremely satisfied’ or ‘satisfied’ with treatment, and higher rates of satisfaction with treatment were observed in the immediate topical compared to immediate oral antibiotic groups.

#### Use of oral analgesics

Use of paracetamol and ibuprofen was poorly reported with only one participant fully responding whether or not analgesia medication was used or not (yes/no) over the 14 days, with the remainder leaving the ‘yes/no’ responses blank.

#### Adverse events

There were three reports of new or worsening of existing symptoms within the first seven days of follow up, one (‘scratching ear’) in the immediate oral and two (‘swollen painful eye with headaches’ and ‘eye discharge’) in the immediate topical antibiotic arms (Table 7) There were three reports of new or worsening of existing symptoms in the second seven days of follow up, one (‘ear leaking again’) in the delayed oral and two (‘sore throat with temperature’ and ‘eye discharge’) in the immediate topical antibiotic arms. The report of ‘eye discharge’ from the first and second 7 days were from the same participant.

#### Serious adverse events

There were no serious adverse events reported. One child attended the Emergency Department but did not require hospital admission.

#### Stool sample microbiological data

Only four (18%) of 22 parents sent stool samples. The research laboratory processed three within 48 hours of receipt, with one sample received 30 December 2019 taking eight days.

### Adherence

In total, seven (33%) were fully adherent to treatment allocation, two (40%) in the immediate oral antibiotic group (Table 8) three (43%) in the delayed oral antibiotic group (Table 9) and three (30%) in the immediate topical antibiotic group (Table 10). Ten (67%) of children in the immediate antibiotic groups (oral and topical) were given antibiotics within 24 hours of randomisation, compared to three (50%) in the delayed oral antibiotic group.

Table 7. Primary and secondary (first 14 day) outcomes

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Immediate oral antibiotics (n=4)* | *Delayed oral antibiotics (n=6)* | *Immediate topical antibiotics (n=7)* |
| ***Primary outcome***  |
| Days (IQR) to all symptoms first resolveda | 6 (4, 9) | 4 (3, 7) | 4 (3, 6) |
| ***Secondary outcomes (first 14 days)*** |
| *Symptom outcomes (days, IQR unless otherwise stated)* |
| Number (%) with all symptoms resolveda at day 3*Yes**No* | 1 (25%)3 (75%) | 3 (50%)3 (50%) | 3 (43%)4 (57%) |
| Time to symptoms first rated “normal/none”, “very slight problem” or “slight problem” | 3 (3, 4) | 4 (2, 6) | 3 (2, 5) |
| Number (%) at day 3 with symptoms rated “normal/none”, “very slight problem” or “slight problem”*Yes**No* | 3 (75%)1 (25%) | 3 (50%)3 (50%) | 5 (71%)2 (29%) |
| Duration of moderate or worse pain  | 3 (2, 3) | 2 (1, 4) | 1 (1, 3) |
| Duration of moderate or worse fever  | 1 (1, 2) | 1 (1, 1) | 1 (1, 1) |
| Duration of moderate or worse ear discharge  | 3 (2, 3) | 3 (2, 3) | 2 (1, 3) |
| Duration of moderate or worse unwell  | 2 (2, 2) | 2 (1, 3) | 1 (1, 1) |
| Duration of moderate or worse sleep  | 2 (2, 2) | 2 (1, 2) | 1 (1, 4) |
| Duration of moderate or worse crying  | 3 (2, 3) | 2 (1, 3) | 1 (1, 3) |
| Duration of moderate or worse eating/ drinking | 2 (2, 2) | 1 (1, 1) | 1 (1, 2) |
| Duration of moderate or worse activities  | 2 (2, 2) | 2 (1, 2) | 1 (1, 1) |
| *Satisfaction with treatment at day 14* |
| *Extremely satisfied**Satisfied**Neither satisfied nor dissatisfied**Not satisfied**Extremely dissatisfied* | 2 (50%)1 (25%)01 (25%)0 | 1 (17%)4 (67%)1 (17%)00 | 4 (57%)3 (43%)000 |
| *Adverse events* |
| Number (%) with new, or worsening of existing, symptom in the first week*Yes**No* | 1 (25%)3 (75%) | 06 (100%) | 2 (29%)5 (71%) |
| Number (%) with new, or worsening of existing, symptom in second week*Yes**No* | 04 (100%) | 1 (17%)5 (83%) | 2 (29%)5 (71%) |
| *Stool sample microbiological raw data at day 14 (N=4)* |
| Processed at research laboratory | 1 | 0 | 3 |
| *First E. coli type* |
| MALDI-TOFb raw scoresc | 2.41 | - | 2.01, 2.2, 2.45 |
| Ampicillin zone (raw data) sizes (mm)d | <6 | - | <6, 14, <6 |
| Ampicillin sensitive or resistant (raw data, % resistant) | R (100%) | - | R, S, R (66%) |
| Ciprofloxacin raw data (mean) zone size (mm)d | 32 (32) | - | 23, 35, 37 (31.7) |
| Ciprofloxacin sensitive or resistant (raw data, % resistant) | S (0%) | - | R, S, S (33%) |
| Erythromycin raw data (mean) zone size (mm)d | 9 (9) | - | 11, 15, 16 (14) |
| *Second E. coli type* |
| MALDI-TOFb scorec | 2.55 | - | - |
| Ampicillin zone size (mm)d | No zone | - | - |
| *E. coli* ampicillin sensitive or resistant | R | - | - |
| Ciprofloxacin zone size (mm)d | 27.1 | - | - |
| Ciprofloxacin sensitive or resistant | S | - | - |
| Erythromycin zone size (mm)d | 9.8 | - | - |

a Defined as ‘normal’, ‘no’ or ‘very slight problem’

b Matrix-Assisted Laser Desorption/Ionization-Time Of Flight form of mass spectrometry used for identifying nucleic acids from biological sources

c >2 is acceptable for diagnostic purposes

d Increased zone indicates increased antibiotic susceptibility (or lower antibiotic resistance)

Table 8. Adherence to immediate oral antibiotic (n=5)

|  |  |  |  |
| --- | --- | --- | --- |
|   | *Yes* | *No* | *Missing* |
| Prescribed oral antibiotic | 5 | 0 | 0 |
| Took first dose on day of randomisation or following day | 4 | 0 | 1 |
| Then took at least 50% of doses as prescribed | 2 | 2 | 1 |

Table 9. Adherence to delayed oral antibiotic (n=7)

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Yes* | *No* | *Missing* |
| Prescribed oral antibiotic | 6 | 0 | 1 |
| Did not start at all | 2 | 4 | 1 |
| Started after waiting until at least the day after the day following randomisation | 2a | 4 | 1 |

a One individual started antibiotics on day 14 so not clear if went on to receive the adequate number of doses over the following 7 days. They have been regarded as being adherent

Table10. Adherence to immediate topical antibiotic (n=10)

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Yes* | *No* | *Missing* |
| Prescribed drops  | 10 | 0 | 0 |
| First dose on day of randomisation or following day  | 6 | 1 | 3 |
| Then took at least 50% of doses as prescribed | 3 | 4 | 3 |

### Secondary outcomes (ear-related quality of life at 3 months)

17 (77%) parents reported ear related quality of life at 3 months using the OMQ-14 questionnaire.(33) Numbers were therefore too small to make definitive comment (Table 11).

Table 11. Secondary outcomes (3 months)

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Immediate oral antibiotics (n=4)* | *Delayed oral antibiotics (n=6)* | *Immediate topical antibiotics (n=7)* |
| ***Secondary outcomes (3 months)*** |
| *Parent reported ear related quality of life at 3 months (OMQ-14 questionnaire)(33)* | *N=3* | *N=5* | *N=3* |
| Physical suffering*Not present/no problem**Hardly a problem at all**Somewhat of a problem**Moderate problem**Quite a bit of a problem**Very much of a problem**Extreme problem* | 2 (67%)001 (33%)000 | 4 (80%)01 (20%)0000 | 1 (33%)01 (33%)1 (33%)000 |
| Hearing loss*Not present/no problem**Hardly a problem at all**Somewhat of a problem**Moderate problem**Quite a bit of a problem**Very much of a problem**Extreme problem* | 2 (67%)0001 (33%)00 | 3 (60%)01 (20%)1 (20%)000 | 3 (100%)000000 |
| Speech impairment*Not present/no problem**Hardly a problem at all**Somewhat of a problem**Moderate problem**Quite a bit of a problem**Very much of a problem**Extreme problem* | 2 (67%)0001 (33%)00 | 5 (100%)000000 | 3 (100%)000000 |
| Emotional distress *Not present/no problem**Hardly a problem at all**Somewhat of a problem**Moderate problem**Quite a bit of a problem**Very much of a problem**Extreme problem* | 2 (67%)001 (33%)000 | 4 (80%)01 (20%)0000 | 2 (67%)0001 (33%)00 |
| Activity limitations*Not limited at all**Hardly limited at all**Very slightly limited**Slightly limited**Moderately limited**Very limited**Severely limited* | 2 (67%)001 (33%)000 | 5 (100%)000000 | 3 (100%)000000 |
| Caregiver concerns*None of the time**Hardly any at all**A small part of the time**Some of the time**A good part of the time**Most of the time**All of the time* | 1 (33%)1 (33%)001 (33%)00 | 3 (60%)001 (20%)1 (20%)00 | 1 (33%)01 (33%)1 (33%)000 |

## Health economics

17 (77%) parents provided resource use information for the two weeks following recruitment. There was little resource use in any arm (Table 12), and because of the small numbers, one patient in the ear drops contributed to nearly all the 14-day resource use and costs for that group (Table 13). Two out of the six patients who had a delayed prescription did not use antibiotics during the 14-days follow-up. Excluding these costs from the analysis reduced the trial medicine costs for this by one third.

Table 12. 14-day resource use by treatment arm

|  |  |  |  |
| --- | --- | --- | --- |
| *Resource use* | *Immediate oral antibiotics (n=4)* | *Delayed oral antibiotics (n=6)* | *Immediate topical drops (n=7)* |
|  | Mean (SDa) | Mean (SDa) | Mean (SDa) |
| Number of GP face to face appointments | 0.25 (0.5) | 0.33 (0.5) | 0 (0) |
| Number of GP telephone consultations | 0 | 0 | 0 |
| Number of practice nurse contacts | 0 | 0 | 0.14 (0.38) |
| Number of NHS111 contacts | 0 | 0 | 0 |
| Number of A&E attendances | 0 | 0 | 0.14 (0.38) |
| Number of outpatient attendances | 0 | 0 | 0.29 (0.76) |
| Number of overnight stays in hospital | 0 | 0 | 0 |
| Number of prescriptions for paracetamol | 0 | 0 | 0.29 (0.49) |
| Number of prescriptions for Ibuprofen | 0 | 0 | 0.14 (0.38) |
| Number of prescriptions for another pain killer | 0 | 0 | 0 |
| Number of prescriptions for other medication | 0.25 (0.5) | 0 | 0.14 (0.38) |

a standard deviation

Table 13. 14-day mean costs (£) by treatment arm

|  |  |  |  |
| --- | --- | --- | --- |
| *Resource use* | *Immediate oral antibiotics (n=4)* | *Delayed oral antibiotics (n=6)* | *Immediate topical drops (n=7)* |
|  | Mean (SDa) | Mean (SDa) | Mean (SDa) |
| GP  | 9.81 (19.62) | 13.08 (20.26) | 0 (0) |
| Practice Nurse | 0 | 0 | 1.6 (4.1) |
| Emergency Department | 0 | 0 | 9.7 (25.7) |
| Outpatient | 0 | 0 | 30.57 (80.88) |
| Prescribed Medications | 0.54 (1.1) | 0 | 1.42 (3.1) |
| Trial medicine | 1.93 (0) | 1.86 (0.18) | 5.45 (0.70) |
| Trial medicine excluding unused prescription costs | 1.93 (0) | 1.29 (1.0) | 5.45 (0.70) |
| Total Cost | 12.27 (20.69) | 14.93 (20.32) | 48.70 (108.73) |
| Total Cost excluding unused prescription costs | 12.27 (20.69) | 14.36 (20.03) | 48.70 (108.73) |

a standard deviation

Table 14. Week 3 to month 3 secondary care resource use and costs (£)

|  |  |  |  |
| --- | --- | --- | --- |
| *Resource use* | *Immediate oral antibiotics (n=4)* | *Delayed oral antibiotics (n=6)* | *Immediate topical drops (n=7)* |
|  | Mean (SDa) | Mean (SDa) | Mean (SDa) |
| **Resource Use** |  |  |  |
| Number of hearing assessments | 0 | 0 | 0.1 (0.3) |
| Number of outpatient attendances | 0.25 (0.5) | 0.29 (0.76) | 0 (0) |
| Number of A&E attendances | 0.25 (0.5) | 0 | 0 |
| Number of overnight stays in hospital | 0 | 0 | 0 |
| **Costs (£)** |  |  |  |
| Hearing clinic | 0 | 0 | 8.40 (26.60) |
| Outpatient | 25.25 (50.5) | 28.86 (76.35) | 0 |
| Emergency Department | 17 (34) | 0 | 0 |
| Total cost | 42.25 (50.61) | 28.86 (76.35) | 8.40 (26.60) |

a standard deviation

A case note review was conducted for 21 patients. Similarly, with the 14-day follow-up there was little resource use, and the small sample size means it is not meaningful to compare the costs between trial arms (Table 14).

## Qualitative

Sixteen primary care staff were interviewed: 9 GPs and 7 non-clinical staff, from recruiting and non-recruiting practices, including one practice that withdrew from the study (Table 15) Some of the GPs had experience of recruiting to the trial and some had experience of getting the TRANSFoRm software working. All of the interviewed GPs were partners and research leads for their practice, with time in practice ranging from 4 to 33 years. The non-clinical staff included practice managers, practice IT leads, a research coordinator and a research nurse (with no clinical role) who had experience of installing the TRANSFoRm software and the processes involved in getting it to work.

Table 15. Primary care staff qualitative interview sample

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Recruiting practices* | *Non-recruiting practices* | *TOTAL* |
| GPs | 5 | 4 | 9 |
| Non-clinical staff  | 2 | 5 | 7 |
| TOTAL | 7 | 9 | 16 |

Nine parents (all mothers) were interviewed: seven mothers who participated in the trial and two mothers who declined to take part in the trial. The parent sample captures some diversity with respect to treatment arm, and child age and gender, but most parent interviewees were from more affluent areas (Table 16)

Table 16. Parent qualitative interview sample

|  |  |  |
| --- | --- | --- |
|  |  | *Parent participants* |
| *Treatment* | Immediate ear drops | 2 |
| Delayed oral antibiotics | 3 |
| Immediate oral antibiotics  | 2 |
| *Home IMD* | 1 (most deprived) | 0 |
| 2 | 0 |
| 3 | 1 |
| 4 | 3 |
| 5 (most affluent) | 3 |
| *Child gender* | F | 3 |
| M | 4 |
| *Child age* | <5 | 3 |
| 5-11 | 3 |
| >11 | 1 |

Eight key themes were developed from the analysis: Trial addressed important clinical question, Clinician views of training materials, Frustrations of trying to get TRANSFoRm to function, Impacts of study on primary care practices, Primary care IT context: key challenges, Barriers to trial recruitment, Experiences of trial recruitment, Reasons for parents declining. Findings are illustrated below using anonymised verbatim quotes, P denotes quotes from parents.

#### The trial addressed an important clinical question

GPs felt that the trial addressed an important clinical question that was relevant to their practice and to their patients. GPs described being unsure about when antibiotics were needed and (in different practices) facing pressure from parents both to prescribe and not to prescribe antibiotics. GPs felt that evidence about effectiveness of the treatment options would support better treatment and better communication with parents.

“*I liked the fact that it’s something that we see a lot and like I say, there’s always this kind of unsureness whether we should be giving these kids antibiotics or not*” (GP08)

“*Parents don’t want to give their children antibiotics unless they absolutely have to so they are quite willing to try some alternatives*” (GP01)

“*we do see a lot of children with ear problems and there is always quite a lot of pressure to provide antibiotics from parents for them. … having either data that says ‘You don’t need to do it’, [or] giving topical drops worked, … would have the advantage … But it’s currently an off license use. So if we could get evidence that that was more supportive of its use, then that would be really helpful for ongoing care for patients*” (GP09)

Normal practice varied between GPs, reflecting a lack of clarity in relation to optimal treatment. Different GPs described normal practice as watch and wait, immediate oral antibiotics and, in some cases, delayed antibiotics.

“*I think I’ve probably been more likely not to give anything actually, just watch and waiting*” (GP02)

“*so normally if they’ve got ear discharge present then we would be starting erm immediate oral antibiotics*” (GP06)

“*if they were completely systemically well and they’ve got a runny ear then I think there might be a bit more of a negotiation about well is it getting better, you know, do you want to hang on for a day or two and see what happens, do you want a delayed prescription*” (GP07)

Views of treatment options also varied between GPs and not all were in equipoise as they did not necessarily view the different treatment arms as equally valid. Some GPs liked the ciprofloxin drops because they were topical and therefore believed to be less likely to cause systemic side effects. Some were familiar with their use for adult patients. One GP raised concerns about the risk of toxicity and another about how quickly patients would be able to access the ear drops. Those GPs whose normal practice was immediate antibiotics were concerned about delaying antibiotic treatment. Several GPs expressed a desire for clear evidence about the best treatment, both to guide practice and to “*validate*” their practice “*to the powers that be*” (GP02).

“*personally I think [Ciprofloxin drops] are good, … I have seen patients with recurrent [infections] who have had treatment with antibiotic drops, on occasions recommended by ENT … so I am sort of aware of it as a practise and I’m sort of comfortable with that*” (GP06)

“*if there was data that said actually giving topical drops worked, then that would have the advantage that you don’t have the systemic side effects*” (GP09)

“*I was always a little bit hesitant to use [Ciprofloxin drops] to be honest, just because of the risk of toxicity … generally if I thought there was perforation I’d stay away from drops generally*” (GP03)

“*sometimes it’s a problem actually getting them, so sometimes we’ve sent them to the chemist and they’ve commented that the chemist hasn’t had them in stock and therefore we’ve been rung up to say you know we want an alternative and I think then we’ve gone to oral antibiotics again*” (GP02)

“*I think it’s risky because… my fear is, is that what if a patient can’t then get in and if they can’t re-present or if their situation’s changed and… so I just feel uncomfortable with this delayed concept*” (GP04)

“*it validates to the sort of powers that be that actually antibiotics, topically, are indicated so we are treating appropriately …and we wouldn’t get the pressure to you know from the kind of prescribing committee, we’d be able to validate the fact that actually we are better treating this with something rather than nothing*” (GP02)

The parents who participated in the trial were happy with the treatment options. The topical ear drops were seen as a good option by both parents who wanted and parents who didn’t want antibiotic treatment.

*“I’m quite intrigued, I quite the idea of the ear drop antibiotics for ear infections, I think they’d be maybe might work” (P02)*

*“I was happy to do it if it helps but also because he’s had so many antibiotics and [I] was happy for him to not have them … to be involved in something which would almost limit the use of them. Because I have been worried about the amount that he’s had to have for his ears over the years. So yeah the idea that there might be another option eventually, … I think that would be really good” (P05)*

*“I thought it was good, I did want her to have some kind of treatment, I didn’t want just to leave it because I think it had been like five days or something at this point. … I thought … there was a two out of three chance that she get a medicine. So I thought that was probably a good idea and yeah it was really easy to do and I was really pleased. And I got the drops … it was really simple” (P04)*

#### Clinician views of training materials

Clinicians described the training videos as detailed and comprehensive, if quite long. The length of the training videos may have meant that fewer clinicians were willing to complete the training to become recruiters, particularly since the expected number of recruits per practice, and therefore the recruitment based payment to the practice, was quite small. Due to delays introduced by the difficulties of getting the TRANSFoRm software to work, some clinicians reported a significant period between completing the training and actually being in a position to recruit.

“*they were very detailed and comprehensive, I seem to remember at least one of them was quite long, … but they were good in terms of guiding me through both the study and the sort of use of the app so what I was doing was watching little bits of it and doing little bits … and then pausing the video rather than watching it in one whole lot so I watched it in piece meal fashion as I was going through, sort of thing… so it did work quite well*.” (GP06)

“*there were quite a few, … anything like that is going to put off some people who don’t have protected time for research … in a practice, you’re expecting maybe five or six doctors … to be recruiting, then that is going to limit, because you know, we just don’t have the time to do that … the problem as well is that it’s not a high recruiting study so if, for example, the practice was going to be recruiting 20 or more patients, then it would be worth watching those videos because you would get, you know, more money for doing that sort of number but I think that you’re only expected to get quite a small number per practice so you might watch videos and do one or two patients and then that… you know forget really*.” (GP01)

“*certainly between the time that I think the training for the online software, so the integrated software rather, and then the erm, the time the study actually went live, it seemed to be a sort of significant gap*.” (GP07)

#### Frustrations of trying to get TRANSFoRm to function

GPs and non-clinical staff involved in installing TRANSFoRm and getting to it work described a long and frustrating process of trouble shooting and multiple reinstallations. Many were initially keen on the idea of TRANSFoRm, as they hoped it would make the recruitment process quicker and easier. However, participants described encountering multiple problems and spending considerable time troubleshooting, seeking support from the trial team and reinstalling the programme.

“*I think as an idea it’s brilliant. … it means you haven’t got piles and piles of paperwork and … paper forms that you’ve then got to somehow get scanned to email through. … it self-populates. … it puts the details in which is time saving. Cos time is one of the big things in general practice*” (GP09)

“*I thought it was really interesting, I was really excited and then it’s made me a bit despondent really*” (GP02)

“*the software didn’t work the first time for us so I had quite a lot of communication with [the trial team] … they’d telephone and speak on the phone about working through different ways of doing it. … to get that to actually work was quite hard*” (Practice Data Manager, ITA01)

“*to be brutally honest with it was quite a nightmare … I’ve probably spent about 10 hours in total trying to install the piece of software on one computer. Um, quite often there would be loads of errors with it installing, with it not working. Um, I’d then have to send emails to the people that were dealing with it. … it’s definitely taken so much longer than what we thought it was going to take.*” (Practice Operations Manager, ITA02)

“*it’s been very frustrating. … communication [with the trial team] has been very good but the problem has been with the REST TRANSFoRm platform. … upset’s not the word but it has taken an awful lot of time to the point where the practices are saying, ‘We don’t want to do this’.*” (Research Nurse, ITA03)

The software had to be installed individually on each recruiting clinician’s computer and limited access to these computers led to delays. It was difficult to get time with a clinical computer, particularly for the early installations which took several hours. If troubleshooting was also needed, then finding a time when the clinical computer and someone from the trial team were available led to delays in addressing problems.

*“the major problem, um, of the installation is actually getting time to get into the GP’s room. … we’re really limited on space so if that GP isn’t in there’ll be a locum in their room … from eight in the morning ‘til 6.30 or seven o’clock at night. So actually trying to get in to have… two hours … is virtually impossible.* (Research Nurse, ITA03)

*“the software was only being installed on one particular PC at our practice … The time we had when his room was available and getting IT involved, was always quite tricky. … we’d have to come back to the office, email, wait for a time when we could speak to somebody … then you're reliant on having to go back into a clinician’s room to go in and … use their PC and … they are seeing patients all day, every day so you're trying to combine your REST study person with me … and then the clinician that’s in the room, to try and combine the three … how long these things take. (ITA04)*

Those who were involved early in the study and were therefore installing an early version of the software felt that it was not sufficiently developed for use in practices. Participants were concerned about the time it was taking from normal duties and the potential risk posed to practice computers.

“*The problem is it was rolled out far … too early with far too many problems and hadn’t been tested widely enough*.” (GP09)

“*It basically felt like it was a prototype, it weren’t like the finished product*” (Practice Operations Manager, ITA02)

“*it has got certainly the admin staff and the practice managers to the point of saying, ‘Do we want this on our practice computers? … is it going to cause more problems?’ … we have not got the time to be spending installing, take hours out installing this platform … it’s a very difficult situation and I’m getting everyone whingeing at me*” (Research Nurse, ITA03)

In addition, during the trial, there was a widespread transition to Windows 10 in primary care practices and this caused some problems. Practices that had installed the early version of the TRANSFoRm software reported that it did not work properly after the transition to Windows 10. It also made trouble shooting more difficult as the person in the practice was using a different version of Windows to the trial staff providing technical support.

“*halfway through signing up for the REST study all our computers were then transferred over to Windows 10 so that caused a bit of an issue apparently … [trial staff] said that… [trial had] programmed all the software for Windows 7 … I think the knowledge on Windows 10 wasn’t there because their systems are Windows 7 … so therefore it was very difficult for me to tell them what wasn’t working on our system because of the difference in the systems.*” (Practice Data Manager, ITA01)

“*when we went onto Windows 10, which was after the first recruitment, it’s not really settled down*” (GP02)

Some participants reported that later versions of the software worked well. The IT Support Manager in a practice that installed the final version of the software described the installation process as quick and easy. A GP who had not been involved in the installation process felt the final version of the TRANSFoRm software worked well and had found it straightforward to recruit patients.

“*And now it nearly works. As in as long as you do this trick to get it to load properly, it works.*” (GP09)

“*I installed [on GP and nurse] PCs and it went absolutely fine, there was no problems with it and it just, yeah installed. … literally minutes … it was absolutely fine. You know it was just pressing next, next, next and finish and, yeah, it was no problem at all*.” (IT Support Manager, ITA07)

“*I didn’t really do the installing. That was done by our research nurse and my practice manager …I do think the actual computer recruiting system I think works really, really well*” (GP08)

In most practices, however, participants described the final version of the software as unreliable and unpredictable. Participants described it working for dummy patients but not real ones, or for some patients or staff but not others, or working in some sites but not others. Participants felt they did not understand why the software appeared to work only in some circumstances and this sense of unpredictability contributed to a lack of confidence in the software.

“*I think one would follow all the instructions and it seemed to say yes, it was working erm, but then it wasn’t when you went into it the next time and lots of shutting down, you kept having to shut down Windows in order to try it again.*” (Research Nurse, ITA06)

“*we tried doing a dummy patient this morning again and it seemed to open up but only randomly… even if we have it set up, it’s going to disappear again and my admin person comes down and sets it all up again and she can’t get it to work intermittently either*” (GP02)

“*it just wasn’t working on [eligible patient] … but it was working on most [patients] that we tried. I have no idea why*” (Research Nurse, ITA06)

“*eventually … we were able to use it but the functionality of what the REST study app was meant to be doing wasn’t happening. … when [GP] was trying to like put in the code on SystemOne the popup was meant to appear… and apparently that popup was never coming up even though it was running in the background. … On some days it would be behind, other days it wouldn’t come up at all. … no apparent reason*.” (Practice Operations Manager, ITA02)

“*I still have this background lack of confidence that its going to if I needed to*” (Research Nurse, ITA06)

#### Impacts of study on primary care practices

The biggest impact of the study was the time taken to get TRANSFoRm working in the already very time pressured context of primary care. This impacted on the GP practices other work, including preparing data for QOF and, in one case, seeing patients. When the time commitment started to impede essential work, then practices started to consider withdrawing from the study.

*“I mean all of the surgeries, all of the, all of the admin staff, practice managers, the secretaries… GPs, there’s not a spare minute in primary care at the moment. … Research in primary care, I think we’re, I think we’re struggling a bit. … There’s such a burden on, on GP time for major problems that research … the GPs would look at the studies and say, ‘Yeah, I don’t have time to do this’*.” (Research Nurse, ITA03)

*“I’ve spent literally hours on this trying to install the software, hours. I think our clinicians have said that, you know, enough’s enough. They don’t want me to spend any more time on it. … they [GP partners] just [got] cross ‘cause I wasn’t doing other things …. I do all the QOF stuff so all the quality registers and things and all the statistics, all the claims. … all that sort of was a bit on hold really.*”(Data Manager, IT01)

*At one point I started to refuse to install stuff because we were having so many problems with what it was doing to our computers … We wanted to wait until they’d got it more sorted because it was just eating so much time. … it was probably towards the end of the QOF year last year, … that I said I wasn’t prepared to put it back on until after we finished the QOF year because I couldn’t risk the machines not working. (GP09)*

When practices had staff with protected research time, this made participation in the project more possible. In most of the practices, the recruiting clinician was a research lead with protected time for research. Some of the practices had other research support staff including research nurses and, in a highly research active practice cluster, a research co-ordinator.

*“had I not been doing [a role with protected time for research] I would not have had the time to persevere and so the trial might not have been able to recruit … from my practice … it was … four, maybe five hours that I spent …. I do have protected time to do it so it does enable me to do things in a slightly different way which I don’t think might be sort of rolled out for other practices … if you think they’ve just got to fit it in in their lunch breaks.”* (GP01)

*“one of them that tried a lot was our research lead. … the other [clinicians] have basically really given up. I can’t get their computers to work now*.” (Data Manager, IT01)

Some participants reported financial costs to the practice as a result of participating in the study. At least one had paid for extra hours for their IT support person to try to get TRANSFoRm to work. Several participants felt that financial support to practices did not compensate for time spent on research activities for this study.

*I’ve worked extra time to do it as well. I’ve, they’ve actually paid me extra to come in and do the REST software so I think that’s sort of annoyed them a little bit*.” (Data Manager, IT01)

*we’ve asked about erm resources for the amount of time that it spent us to install this software and provide the feedback that they’ve asked for and answered the questions they’ve asked for … the practice has actually lost quite a lot of money in terms of their time by trying to engage with this and that just puts people off. … we do expect our costs to be covered. We do research cos we’re interested in research. If we were interested in making money we would do pharma, but we don’t. But we are interested in not making a loss on it and not making a significant loss on it which is what we’ve done with this.* (GP09)

#### Primary care IT context: key challenges

Participants identified challenges with practice, CCG and NHS IT that contributed to the difficulties in getting TRANSFoRm to function.

At the practice level, there was limited IT capacity and expertise. There were issues with outdated hardware and software and with the way in which individual GPs had adjusted SystemOne settings. There was the varied IT expertise and capacity in individual practices with many reliant on a GP, manager or administrator with only modest knowledge of IT. Computer admin rights (needed to install software) were usually restricted to a small number of staff and not necessarily those with time or responsibility for setting up research studies. This meant that in many practices the person tasked with doing the work to get TRANSFoRm to function often struggled with the tasks and with understanding the various problems encountered.

“*[TRANSFoRm is] designed for really up to date computer systems and primary care is running on ... old equipment and it just couldn’t cope with it … not only is it old but it’s very old [and] not all on the same Windows*.” (Research Nurse, ITA06)

“*the user guide was relatively comprehensive, but I would say not written for a user…that had basic IT skills, I think what they were asking for somebody who was fairly IT literate to install the software, which I certainly wasn’t. … We don’t have a particular IT person that can just go along and install…this sort of software*” (Assistant Practice Manager, ITA04)

“*we are a fairly small practice … it was pretty much … me on my own … just trying to go through the installation step by step to work out where it wasn’t working and then trying to work out why so, trial and error*” (GP06)

“*we’re not all IT proficient and that’s the problem. … large practices they do [have IT expertise] … but they don’t necessarily have the admin rights. … these [small] practices don’t [have IT expertise]. So it’s the practice manager or … the secretary or someone who does it*.” (Research Nurse, ITA03)

“*we didn’t locally have full admin rights. Well the Practice Manager did but you know, to get her to sit down for a couple of hours and set it all up was very difficult, she didn’t have a couple of hours.*” (Research Co-ordinator, ITA05)

There were issues with obtaining help from outsourced CCG funded IT support. Practices all had some IT support provided by an external body, sometimes a private provider and sometimes a CCG or NHS provider. Five different providers were mentioned by our small number of participants and IT support arrangements varied with respect to whether the external body held exclusive admin rights for practice computers or supported research IT. Several practices reported that their external IT support provider would not assist because the software was not on the CCG approved list. When they were asked to provide support, these external bodies often raised concerns about the unknown TRANSFoRm software, were usually unfamiliar with software for research projects and slow in providing support due to limited capacity. Only a research co-ordinator at very research active practice reported getting help easily, which she attributed to a good relationship with a particular person.

“*we’re not sort of in charge of our own IT, the IT goes out to another company … our IT people who are [company name A], they’re not really supposed to give admin rights to anybody in a practice … [company name A]will not get involved with other people’s software. …they have a list of software that’s allowed on the system and if we’re going to put some other software onto it they will not support us installing that software”* (Practice Data Manager, ITA01)

“*we do have [company name C] but I didn’t get them involved in it…’cause … [name C] wouldn’t help with it anyway. … because it hadn’t been signed off by our CCG so we shouldn’t be installing it on our computers*.” (Operations Manager, ITA02)

“*there’s been problems and we’ve had to go to our CCG IT team. And I’m just looking at an email that’s come in this morning and their IT team are saying, ‘What is this application? Is it a trusted…?’*” (Research Nurse, ITA03)

“*[company name D] so they're IT, they're all NHS staff but they're a helpline, so you ring them erm, with an IT queries,… they were very dubious actually,[about TRANSFoRm] … I'm on I think my third or fourth call now with our IT about it. [It] wasn’t always easy to try and coordinate them ringing with then trying to install the software.*” (Assistant Practice Manager, ITA04)

Some practices reported that they had to obtain permission from their CCG before installing software on their practice computers. The transition to Windows 10 during the trial was linked to the loss of practice level admin rights over computers in some CCG areas. Whether or not practices retained some admin rights over their computers (and therefore ability to install software) varied across recruited practices. When practices had to obtain permission from their CCG to install software, this could be a lengthy process. CCGs raised questions about the risk that this unknown software could corrupt NHS software or practice computers and concerns about patient data crossing the NHS firewall. The centralisation of management to the CCG was seen as supporting initiatives such as the single domain, which allows better sharing of patient notes between different types of practitioners in primary care. However, it also had the unintended consequence of restricting the installation of study specific software. While some practices appear to able to install software freely, most reported having to defer to and wait for CCG approval. One practice reported that their CCG had required modification of the software to increase data security before permission was given.

“*we had a big change at our practice erm, something called single domain which basically means that they’ve taken a lot of admin rights away from a lot of the users including me… cause I think it was becoming problematic across the practices that you know, we had free rein really. And that’s going to cause a problem with things like REST because we can’t install it, so you give us a set of instructions and we won’t be able to do it because it has to go to our localised IT who has to verify they're okay with it first.*” (Assistant Practice Manager, ITA04)

“*the CCG took it upon themselves to be responsible for all of our hardware and software, so when Windows 10 came for the whole of the CCG, they then took charge of everything really, which in a way makes sense because they paid for it and therefore they should control it and the flow of information that’s available and try to link it all up with other bits of the NHS, but as a result things … fell by the wayside, unfortunately.*” (GP05)

“*because of the way that the NHS is set up we had to get firewalls opened, which wasn’t something we were told about in the beginning, to enable the software to contact [trial database] and then also for them to contact back through to our software so basically you had to go through the firewall through a different port. And because we, we’re not sort of in charge of our own IT, the IT goes out to another company so that was quite complicated at the beginning, having to go through these firewalls by logging it with our IT and then our IT doing it and that took a while. So that was the first sort of big issue we came across.*” (Data Manager, ITA01)

“*I think [the CCG] are quite – lax might be the wrong word, but we can install software and we do install software. So we’ve installed software for other research studies with no problems*.” (GP09)

“*we were all set to go and then we… needed to change our operating system … Windows 10 so the original… [TRANSFoRm] downloads would no longer work … to get them to re-work … we couldn’t do it ourselves any more, we had to get the CCG computer boffins in to do it for us, they didn’t want to do it because they said its software may corrupt the NHS software and they wanted more assurance from higher levels than me that it was all safe to go, soooo… I got cross the told them it was all, it had been approved at high level, … co-ordinated at committee level and approved and was being used elsewhere and they shouldn’t be so silly … so they then did come and put it on for me, so it’s now up and running*” (GP05 – with role in CCG)

“*[I] installed the software once I had permission from the CCG and that took [from] July/August … until December … the CCG felt they hadn’t got enough information from the installation guys … to be satisfied about the security aspect of the data that’s being transferred … the [study] IT Engineers [tested] an encryption patch… [and] in December 2019, it was approved for installation… it’s just checking the security side of things, just make sure we’re not going to get any viruses... it’s about data protection, you know they want to make sure that no patient identifiable data is going to be sent over for the studies*.” (IT Support Manager, IT07)

#### Barriers to trial recruitment

Trial recruitment was reduced or slowed by the problems with the TRANSFoRm software. Several practices described identifying eligible patients but not being able to recruit them to the study because the software did not work properly. In some practices, there was a long delay while staff struggled to get TRANSFoRm to work before clinicians even started trying to recruit patients. Some practices decided to withdraw from the study before any patients had been recruited because of all the time taken to try to make the software work.

*“last month there’s been four we’ve missed and all because the software just does not open up, … I had someone in front of me on Thursday whose mom was really interested in doing it, I couldn’t even do a decline, and we just couldn’t get it to work and I tried, honestly I must have spent about 20 minutes I think, trying to sort it out and I had to move on really.*” (GP02)

*“We’ve missed recruiting patients to the study because we couldn’t get the software working. We’ve had them in the consulting room agreeing to do the study but we just couldn’t get the software to work so therefore … we’ve had to abandon it. So there was a possibility of at least seven or eight that we couldn’t get because I’ve gone in and sat with the clinicians as well to try and get the software to work. … it’s not that we’re not wanting to, it’s not that we’re not trying. It’s the software that’s not working*…” (Data Manager, ITA01)

*“I think that’s probably why there’s no recruitment because the actual software itself wasn’t doing what they needed to do and then if they’re in an appointment they obviously don’t have the time to figure it out so they just move on to the next patient. … the doctors… they don’t have the knowledge to quickly figure things like that out … especially if it’s software that they don’t usually use*.” (Operations Manager, ITA02)

*“we've taken a massively long time to recruit four patients…. we should have done eight in a third of the time, probably would have done if the software worked*.” (Research Co-ordinator, ITA05)

Eligible patients were sometimes missed because they were not seen by a clinician able to recruit to REST. The processes for channelling eligible patients towards a recruiting clinician differed across practices. This was partly due to differing processes for dealing with same day appointment requests for acute illness. Some practices had minor illness nurses who would usually see all children with suspected ear infections. Some practices triaged all patients requesting same day appointments and these might be seen by 1-2 duty clinicians or any clinician with a free slot. Study recruitment problems arose when these normal processes channelled a potentially eligible patient towards a clinician who was not able to recruit to the study. Admin staff and triaging clinicians responsible for booking patients into appointment slots did not always remember to book potentially eligible patients with the few recruiting clinicians. Where an eligible patient was seen by a non-recruiting clinician, there were various *ad hoc* arrangements to redirect patients to recruiting clinicians, but these were probably impractical and there were no accounts of this happening in practice.

*we’ve got minor illness nurses and the minor illness nurses don’t really get involved in research as much … the problem is that if someone rings up with a cough or cold, all that kind of stuff, they are being put into the minor illness slot … we tried to actually put REST Study slots into my clinic so that if anybody rings up with an earache, … put them in here, but … I’ve had those slots up and running and I think it’s not even been used once … but we know that these guys are coming through because they have gone and seen the nursing team, yeah? GP03*

*reception are made aware that if they have a child with a runny ear to try and book them in with myself or the other GP in question where possible, where not though, and this has happened, … a couple of times, that someone else [sees an eligible patient] they send me an instant screen message to say … do you want to see them … and then depending on… how my appointments are looking, I might say yes that’s fine, or I might say … could you see, patient Y for me instead and then we sort of switch patients if you see what I mean…(GP06)*

*whoever’s doing surgeries will have some appointments added on at the end for same day so we don’t do triage or anything else… the nurses will do the same, … they might see … children with coughs and colds…the receptionists have an aide memoire to say any child with…earache, of the right age, and they’ve had any discharge at any time that they should be booked in with me (GP05)*

*We can’t do too much opportunistically, I mean people coming to urgent care, they struggle to get an appointment in the first place … our Advanced Practitioner might not be on the delegation log but one of my GPs is, but they're seeing somebody else (ITA05)*

Some eligible patients were missed because recruiting clinicians were not available when the patient needed to be seen. Some recruiting clinicians only worked part time and were only able to protect certain time slots that did not necessarily coincide with when patients needed to be seen. A participant from a large recently merged practice described the challenge of keeping triaging clinicians primed to recruit to the study when they faced long lists, multiple study reminders and were not even sure of being able to book a patient in with a recruiting clinician.

*I think there may have been a couple of kids with discharge who might have seen other GPs. You know, cos I only work part-time. (GP08)*

*nothing came in in the morning, and then I had a full booked surgery in the afternoon … somebody came in in the afternoon … they came in at 4.30 which is… right in the middle of my surgery that was running late anyway, … nothing’s come in this morning, I had protected time this morning, GP01*

*now we've merged, we've got 25 GPs, six partners but … lots are part-time… so trying to keep it at the forefront of their mind, those images on the computer screen that they have got them every morning in a way you just get used to them being there, you don’t actually look at them…they come and face an absolutely hideous list, phone calls every morning … there were two days when there wouldn’t have been a slot, if they had remembered, they couldn’t have found a slot which is probably make them think, oh, well I actually remembered and then I couldn’t book them in. (ITA06)*

There were a limited number of clinicians who could recruit to the study in each practice and this contributed to missed recruits. There seemed to be several reasons for the limited number of clinician recruiters per practice. In many practices, only the research lead and perhaps one other clinician completed the training to become a recruiter to minimise the training burden on practice staff. It is likely that the time it took to install the TRANSFoRm programme also contributed to practices only installing on a limited number of computers.

*I could recruit, none of the others did the training on the basis that it was most likely that the [trained] nurses would do it … when you’re not recruiting massive numbers, if you have too many people able to recruit, nobody does it very often, so it just takes everybody ages. (GP09)*

*“What we can’t do is install it on everybody’s system … we've got about 20 studies we might be doing at one time so you have to pick and choose your staff of who’s going to be involved (ITA05)*

*“we have it installed on mine and the other GP … who has the research experience … and the administrative machine, it’s not running on the other clinician’s machine… so not everyone’s recruiting, just the sort of people who know about the study. (GP06)*

The nature of the target patients also presented some barriers to recruitment. Acute infections are seasonal and by the time the TRANSFoRm software was working in most practices, the winter season, when patients are more common, was over. Cases that fit the criteria for inclusion in REST were relatively rare. One research nurse described studies evaluating a new medication for acutely unwell children who attend with a parent (and often other siblings) as one of the hardest studies to recruit to.

*in the summer we don’t see that many, in the winter, probably one to two a week… as a surgery… I’m trying to think, probably about two a week, something like that. (GP02)*

*it started at a time in summer where there wasn’t very much happening [mmm] and I think that’s taken a lot of momentum away,(GP03)*

*anything that involves a child that’s unwell, the parents have got other children with them, you know, younger children… children’s studies are harder straight off cause the parent and the child are involved rather than just an adult and if it’s a child who’s already a bit anxious then that makes it harder so I think the children’s ones, where its opportunistic recruitment are probably the harder ones we do … and if it involves medication, its more complicated straight off. I suppose it is one of the hardest scale of ones that we do in general practice, I'm afraid our current issue is time. (ITA06)*

#### Experiences of trial recruitment

When clinicians had successfully recruited, this seemed to be associated with parent interest in the study and with consultations by ‘relaxed’ mums for relatively well children that had time for recruitment. Clinicians reported positive responses to the novel treatment (ciprofloxin ear drops) and to the study processes.

“*well parents were happy that something was being looked at … those parents that we've seen… its not … the first time they’ve been in, they're coming in regularly with the same child saying ear pain and discharge … And some of them are very reluctant to have antibiotics but all of them want some help. You know they all seemed to like the idea of trying topical drops.*” (Research Co-ordinator, ITA05)

*both of [the recruited children] were … it made it easier… both children were actually incredibly well, but there was loads of gunk coming out of their ears erm and they both had very laid back mums. … I said to both of them, you know, ‘There’s this trial going on looking at the different treatments, obviously I will examine your child and if I disagree with what you’re randomised to you know, we can decide not to go along with it. … I think [the first mum] really liked the follow-up that she had with the trial team … all the leaflets with the advice and things like that … I think it was helped that they were relaxed mums and they obviously weren’t in a massive hurry and – yeah. It made it easier (GP08)*

*mom was pretty excited to be part of it so I think that was really quite nice… She was randomised to cipro … the ear drops…She was fine with it, I think the patient information leaflet was very good, you know, so that was excellent*” (GP03)

Recruited parents described study processes as straightforward. They had a clear understanding of the study purpose and found it easy to provide follow up data.

*I think everything was really well explained and the actual medicine that she got was really easy to use, the questionnaire was really simple, it was really easy to send stuff back. No it was absolutely fine. (P04)*

*the nurse did explain to me as much as she could but [child] was quite … unsettled … it was a bit erm difficult to kind of grab all the information that the nurse had to give me but the pack was quite comprehensive … it did have quite a lot of information and leaflets about what the study was about so I had the chance to read a bit about it when I got home so and I had a call from one of the ladies involved in the study as well pretty much the next day … which was good because then you kind of get their reassurance of the study itself (P07)*

*I would have been happy with… any of [the treatment options], because they said if you’d have had nothing then if he started to get a … higher temperature or got really unwell then they would … look at him again … if he became really unwell. So they said that as it was at the moment he was happy for him to either have antibiotics or to not have it. … They said at any time I could sort of take him back in and have him checked. (P05)*

#### Reasons for parents declining

Of the two parent decliners who participated in an interview, one declined because she wanted antibiotic ear drop treatment and one because she did not want her child to have antibiotics. In the former case, the child had a history of ear problems and the parent had experience that led her to perceive ear drop antibiotics as more effective than oral antibiotics for her son’s ear infections. In the latter case, the parent was aware of the drive to reduce unnecessary antibiotics, was told by the recruiting clinician that he wouldn’t normally give antibiotics for her child’s symptoms and she didn’t want her child to take something that wasn’t needed. Recruiting clinicians described parents declining to participate because they didn’t want to have to

“*he’s had some ongoing problems with his ears … about a year ago he had like a runny ear for quite a long time and he went on an oral antibiotic and it didn’t clear it up. And it carried on for probably about two months where … when I went back to the doctors and they found in his records I think from the ENT that he should have the drops in his ear. And when he did have the drops it cleared it up within about a week so when they asked me to do the, you know, be part of the study they said it was a randomised, where they just leave it or have the drops or have the antibiotics. And because I knew that that had been really effective with him last time and I didn’t want it to drag on for a few months like it did last time I just asked if they would give the drops. … I think if it had been my daughter who’s not had any ear problems, you know, or recommendations about what she needed I definitely would have done the whole study*.” (PD01)

“*the reason that I didn’t want to participate in the study because if there was no study she wouldn’t have got any medication for it at all. So it did seem a bit odd that…if she participated in the study then she’d be given antibiotics I thought the idea was that you only get antibiotics when you really, really need them. … The doctor had said that at this moment she didn’t need anything. … I didn’t want her taking something*.” (PD02)

“*we did start to use the software and go through some of it sort of and then I showed them the leaflets about it and mom just started to look more and more doubtful about the whole thing as we went on, so she showed some initial interest and sort of said, yeah, ok maybe I’d be interested in that and then as we talked about it and what she might have to do in terms of having a phone call, doing a sort of diary and things like that, she just looked more and more doubtful about it, to the point where you thought no she really doesn’t want to do this and I sort of said look, … it is up to you, you don’t have to and she said no, I think probably not, so it was a more slow sort of build to her saying no I’m not interested in it*.” (GP07)

# CHALLENGES AND RECOMMENDATIONS

This chapter summarises the key study challenges and lessons learned. These are relevant to many primary care studies, but particularly those involving large numbers of sites and those intending to use (or develop for use) electronic trial platforms. The lessons learned are presented as ‘recommendations for future practice’, are written in *italics*, and grouped by those responsible for the activities: site identification, site set up, site training, platform development, platform installation, troubleshooting, platform function monitoring and data management. Finally, there are two recommendations for national stakeholders, including DH&SC and NIHR.

## CRN coordination of site recruitment

From a study perspective, CRN facilitation of site set-up was frustrating. The CRNs were reluctant to tell the study team which practices had been invited and how many times, and it there was little feedback regarding why practices did not wish to participate. The study team was clear that there was no prerequisite for sites to be ‘research active’ as the TRANSFoRm software was intended to guide even novice recruiters through recruitment. Indeed, for some studies recruiting via research naïve sites could be important to ensure generalisability of the final study sample.(72) In this case, the team sensed the CRNs were only approaching research active sites.

*Recommendation*

1. *CRNs should keep logs of which sites have been invited, when and how many times. These should be shared with study teams, in order to populate CONSORT flow diagrams and allow a description of the generalisability of the recruiting sites.*

## Site set-up

We worked closely with the Sponsor to use risk adapted site set up and study conduct approaches, aiming to reduce burden on GP practices. Despite this, there were still long delays securing the required documentation from the GP practices, particularly delegation logs and CVs for which the Sponsor required wet ink signatures. Despite clear instructions, these were regularly incomplete or incorrect, with signatures missing. Since staff were inevitably busy, having to return a document because of a small mistake often resulted in several days/weeks of delays, and the paperwork was often forgotten and needed to be chased. This added to the workload of the study team who were often chasing multiple sites for various documents/amendments to documents and prevented the site from receiving green-light from the Sponsor. The study team kept a spreadsheet record of all documents received from each site within each of the 15 CRNS. A PDF/word copy of each document was stored electronically in dedicated site folders. Although this system worked to a degree, a study of this size would have been better employing a more robust electronic document management system that could highlight missing or wrong documentation. This would have made it easier for the study team to chase sites.

*Recommendations*

1. *Sponsors should consider accepting electronic versions of delegation logs with e-signatures. These should be designed such that submission of incomplete logs/ CVs is not possible.*
2. *With large distributed trials with many sites a robust electronic data management system to track documentation should be employed.*

## Site training

Because of the number of sites expected to be needed for the REST study, it was decided that online training (see [www.rest.healthcareandvideos.com](http://www.rest.healthcareandvideos.com)) would be a more appropriate and efficient way of carrying out study training. It was predicted that busy GPs and nurses would complete the training at times convenient to them and this would expedite opening to recruitment. Unfortunately, this did not prove to be as an efficient as hoped: clinician time is not ring-fenced for remote training as it would be during face to face training; and staff sometimes took weeks or months to complete online training. Without the face to face engagement it was difficult to encourage site staff (some of whom the study team had previously not worked with) to complete the training in a timely manner. With more studies employing remote training mechanisms, research active GP practices need to be encouraged to allow time for staff to complete remote training.

*Recommendation*

1. *Where online site training is used, studies should provide training via a website that provides automated reminders and notifies the Sponsor and study team when training is complete.*

## Electronic platform

### Development

TRANSFoRm was a novel electronic platform that was considered necessary for the REST trial as most GP practices would only see a few cases of AOMd each season. The vision was that the system would ‘take the hand of the clinician’ and guide them quickly through eligibility, randomisation, baseline data collection and randomisation – all electronically integrated within the electronic medical to auto-populate relevant data thereby saving time, minimising data entry and minimising data entry errors. The platform was considered key to facilitating recruitment and was designed to support many sites, reducing burden on the trial team and increasing the quality of the data.

In the event we seriously underestimated the variety of computer configurations in English GP practices, the complexity of IT support arrangements, the difficulties of integrating and ensuring smooth platform function, and the resources required to overcome these obstacles. These led to significant delays to the first GP practice opening, delays in recruiting further GP practices, delays in site set-up and ultimately reduced participant recruitment.

Failure of the TRANSFoRm platform to provide data regarding which sites were and were not managing to recruit meant the study team was virtually blind to, and unable to support, site recruitment activity. We have minimal information regarding the frequency of pop-up triggers (Table 3, page 62) and know only of 30 children being invited to participate (Figure 6, page 39). Compared to our recruitment assumptions (Table 1, page 27), 30 invitations would have resulted in 2 or 3 children recruited. We are aware of instances where sites had potentially eligible children available to recruit but were unable to recruit due to TRANSFoRm not being available. Practices found this frustrating with some sites withdrawing from the study.

Detailed platform specifications were drafted (see Detailed TRANSFoRm technical specification for REST v1.4). Some were REST specific, while others could be applied to other studies. For example, some were intended to provide estimations of the generalisability of the final trial sample, in relation to the characteristics of potentially eligible children invited but declining. Some TRANSFoRm software components had incompatibilities with certain versions of the Windows operating system and this made automated updating of TRANSFoRm’s DNC difficult. Other software would be updated, such as EHR software, without prior warning with updates proving incompatible with TRANSFoRm software.

*Recommendations*

1. *Electronic trial platforms should be used to harness the unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where the key ‘drop offs’ are in the recruitment process from presentation to consent.*
2. *All necessary platform preparatory activities and required resources should be clearly defined, taking care not to under-estimate either*
3. *The skills needed to set up a trial platform, and to set up a trial are distinct and complementary. Ideally teams should be co-located to ensure platform specifications meet individual trial requirements*
4. *Platform software needs to be compatible with all practice software systems*
5. *Closer integration with EHR providers would prevent incompatible updates [NB. this could be obviated if national criteria were agreed or if the trial platform was integral to the EHR].*

### Installation

Due to lack of standardised set of security requirements for software in general practice, some providers requested further assurances from NHS Digital, and additional security features added to the system. We engaged with NHS Digital, and NHS X, who confirmed they consider our software to be safe for installation but declared any detailed technical audit to be outside of their remit and the responsibility of EHR providers. This required us to negotiate approval with the EHR providers, TPP and EMIS.

While IT support is formally handled by the CCGs, it is often outsourced to independent third parties. The installation of software such as TRANSFoRm is typically not covered by the contracts governing these outsourced relationships, and neither were the criteria clear to establish the safety of new software prior to practice installation. Some third parties quoted prohibitively expensive costs to support installation. These issues only came to light after the practices were recruited. The REST team worked hard to obtain CCG approvals from many areas, but some took months with key areas such as the Nottinghamshire Health Informatics Service (NHIS) Change Advisory Board (CAB) and the Devon CCG arriving too late.

*Recommendation*

1. *Project teams need to work closely with EHR providers and CCGs from the study outset to agree the software deployment process and the validation criteria required [NB. this could be obviated if national criteria were agreed].*

In addition to CCG approval, installation agreement was part of the site agreement meaning national and CCG level approvals were required *before* practices could sign the recruitment contract, which included identifying the site personnel involved, machines, and training.

*Recommendations:*

1. *A pilot install incapable of being used for recruitment and therefore not a site agreement requirement) should be performed on one computer in each practice, tested, and left to run for a week, before installing software on to other machines*
2. *Where software re-installation is required, it must be done in a way which does not disrupt the work of the practice.*

### Troubleshooting

To try to assist the under-resourced TRANSFoRm team (based in London), some trouble-shooting tasks were re-assigned to the RCT team (based in Bristol). However, but this was less effective than hoped because the Bristol team did not have the IT skills and experience to efficiently address the challenges, leading to further delays.

*Recommendations*

1. *Electronic study platforms require teams dedicated to: (i) development; and (ii) troubleshooting.*
2. *Careful consideration should be given to who is responsible for troubleshooting – while it may seem obvious this is done by the trial team (since it involves interacting with sites), it requires awareness of platform function and may therefore be better provided by the platform development team*

### Monitoring function

No one in the team anticipated the importance of a dashboard reporting real-time platform functionality. This can be likened to the real-time status reporting of the London Underground tube system. Much of the time, neither the TRANSFoRm team nor the trial team were aware that the platform had stopped working, either across all sites, or at specific sites. Even now we cannot estimate the proportion of time during which, nor the proportion of practices at which, a fully functioning platform was able to facilitate recruitment. Functionality could be threatened by a number of reasons, including problems and updates in: TRANSFoRm; the host EHR system; the Windows operating system; or practice network configurations.

*Recommendation*

1. *Electronic trial platforms would be best served by a dashboard function to monitor and log platform functionality in real-time, providing real-time alerts and diagnostics for reduced function, and logging functionality across time and space.*

### Data management

At the project outset, no agreement was made on the format and type of data to be sent from the study database to the trial team.

Recommendation:

1. *The format of the final dataset to be extracted from the study database should be pre-specified to ensure appropriate data format and avoid the submission of linked clinical and personal data.*

### National stakeholders, including DH&SC and NIHR

Many of the above challenges and solutions may be better addressed nationally via a single coordinated management and implementation group. This would be particularly helpful for the NHS IT related challenges, since NHS IT will continue adapting to meet future NHS needs and unless research is considered part of these changes, future software study platform developers could find it similarly difficult to ‘bolt on and hold on’ software to these changes.

We consider the key national stakeholders should include: DH&SC; NHS Digital; NHS X; NIHR; senior researchers with trial and observational study experience; EHR providers such as EMIS® and TPP SystemOne®; MHRA; CPRD; and GP IT Futures framework.

The prize is rich and the opportunity clear: to lead the world in the delivery of pragmatic research that quickly and efficiently develops highly generalisable new knowledge to improve patient care. The current SARS-CoV-2 pandemic perfectly illustrates the need for, and value of, infrastructure ready to quickly respond to the changing health needs of the UK population.

In our view, the NIHR and other funders need to be part of the solution but cannot solve it alone. We are delighted the NIHR HTA accepted our argument that REST needed to be underpinned by an electronic research platform, but in doing so they took a risk that was outside their remit – to support the time needed to develop the platform. We are deeply regretful we were not able to fulfil this ambition.

*Recommendations*

1. *Research funders need to formally recognise the potential of electronic study platforms if they wish to put the NHS at the leading edge of pragmatic research globally, allowing the delivery of new, near-real-time generalisable knowledge, and providing unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where the key ‘drop offs’ are in the recruitment process from presentation to consent, that influence final study sample representativeness.*
2. *The NIHR and research funders should consider convening a meeting of national stakeholders to define a strategy for the development, implementation, and ongoing management of electronic study platform software.*

## Trial management

The TMG and co-Chief Investigators were aware throughout the study of the delays to the delivery of the TRANSFoRm platform despite repeated reassurances that the platform was almost ready. The co-Chief Investigators found it challenging to manage these delays, particularly given the academic nature of the collaboration with the partners responsible for platform delivery, and the need to maintain good working relationships. While we feel the latter has been achieved, we reflected with our host (BNSSG CCG) and Sponsor (University of Bristol) on how to manage delays in future studies. This meeting resulted in the host proactively communicating their role of enforcing contractual obligations to all their hosted studies, which includes engagement with project managers between management meetings, and the creation of the CCG Contractor Escalation Guidance document (see CCG Contractor Escalation Policy ) which explains and guides the assistance the Host can provide to CIs and Project Managers with underperforming collaborators.

# DISCUSSION

## Summary of main findings

### Trial

To our knowledge, this is the first time a CTIMP has been conducted using an electronic trial platform in the UK. We planned to establish 175 sites to recruit 399 children. By study closure, 122 GP practices from 12 CRNs had expressed an interest in supporting the study of which 71 confirmed participation, 61 received sponsorship, 44 opened to recruitment with TRANSFoRm installed on 72 clinical computers, and seven sites randomised 22 children.

Although the main reason for poor recruitment was the delayed and intermittent functioning of the electronic platform, AOMd presentations were also lower than usual seasonally adjusted averages, contributing an estimated 25% to under-recruitment.

Despite the ‘hands off’ nature of recruitment, randomisation and the use of standard NHS FP10 prescriptions for treatment, baseline data were available in 21 (95%) of children, all children were given treatment as randomised, 38% fully adhered to the treatment, and the symptom based primary outcome was available at the 14 day follow up in 17 (77%) children. The number recruited were too small to perform comparative analyses and draw definitive conclusions regarding effectiveness, cost-effectiveness or safety, but we observed all bar one symptom duration (including the primary outcome) was shorter in the immediate topical compared to immediate oral antibiotic groups, and that parent satisfaction with treatment was higher in the immediate topical vs. immediate oral antibiotic groups.

### Electronic trial platform

Delays in setup and functionality of the TRANSFoRm electronic trial platform function led to a vicious cycle of increasing challenges resulting in critically low recruitment and early trial closure. Key performance challenges included: (i) under-estimating the technical challenge of integrating platform and EHR software; (ii) under-estimating the resources required to troubleshoot resulting problems; (iii) the need for repeated site platform reinstallations, sometimes due to unannounced changes to EHR software; (iv) multiple and complex site IT security arrangements, often involving third parties without contracts covering research; (v) failure to foresee the need for a platform ‘dashboard’ function resulting in the TMG being unaware when the platform was/was not functional; and (vi) progressively reduced site staff motivation to re-install and use the software. That said and acknowledging it was ‘too little too late’, when the electronic trial platform was operational, clinicians reported strongly liking its features and that it assisted recruitment as intended.

### Qualitative

Qualitative clinician interviews found the trial addressed a question of importance to clinicians and parents, and that when the platform functioned it was liked and worked as intended. However, site staff reported the software not working properly for long periods, resulting in potentially eligible patients being missed. Moreover, getting the software to work placed significant burdens on GP practices, diverting staff time from core activities.

The IT arrangements in primary care practices were varied and changing, with limited capacity, expertise and support. While some practices had employed an IT expert, many relied on non-experts with limited knowledge or training to provide internal IT support. This limited IT expertise within practices made it difficult for them to work with the software development team to diagnose and solve the problems with the software. External IT support, which was provided by experts, was often not available for research. Administrative rights over practice computers, which were needed to install TRANSFoRm, were not always held by staff within practices. Practice IT arrangements changed during the course of the trial so that practices that did have administrative rights for the first installation of TRANSFoRm did not have administrative rights for subsequent installations and had to apply to their CCG for permission and support. Some of the changes to the practice IT arrangements was driven by new legislation such as GDPR and initiatives to allow better integration of primary care medical record systems with others such as out of hours services. The changes in service of those broader NHS objectives restricted the use of specialist project software on practice computers.

## Strength and weaknesses

### Trial

To our knowledge, this is the first RCT to investigate the clinical and cost-effectiveness of immediate topical or delayed oral antibiotics compared to immediate oral antibiotics (standard care) for children with AOMd without grommets, and one of the first to attempt this using an integrated electronic trial platform. The qualitative evaluation provided rich contextual evidence regarding the advantages of, and problems with, the TRANSFoRm platform.

The overriding weakness is the failure to recruit enough children to address the research question.

That said, when functioning, the electronic trial platform did assist with within-consultation recruitment, demonstrating that it (i) can work and (ii) its multiple advantages.

First, the system did support the identification, baseline assessment and consenting of children. Clinicians provided treatment as randomised for all children cases and most parents of recruited children provided symptom duration data. One child with a visible tympanic membrane was recruited but should have been excluded. This cannot be attributed to the trial platform, but could have been prevented if the platform alerted the clinician to the presence of an exclusion criterion. The recruitment reminder ‘pop-ups’ were triggered by Read diagnostic codes, but would have been more sensitive had we also used Read symptom codes.

Second, as previously rehearsed, an electronic platform could provide unprecedented evidence regarding the generalisability of the final sample, support the recruitment of a very large number of ‘real-world’ pragmatic studies, ensure improve baseline and follow up data entry efficiency and accuracy, and ensure studies meet many regulatory requirements.

While the main outcome data attrition rates were acceptable, we note the low rate of stool collection at day 14, and the poor recording of analgesic use. We are also aware that one child was recruited with otorrhoea possibly related to a foreign body. This should have been an exclusion criterion. Regarding treatment fidelity there were high levels of agreement with allocated arms with no crossover between arms. Although adherence appears low this of less concern when participants are randomised to a treatment strategy in an open trial since adherence (antibiotic use) is likely to mirror actual management in real world settings. It is for instance recognised that antibiotic use is higher where the prescription is supplied in consultation and when following a delayed strategy outside the trial context.(71) (73)

### Qualitative

The small number of recruited parents and early shut down of the study due to the Covid-19 lockdown constrained recruitment to the qualitative study. However, sufficient ‘information power’ was achieved for the core themes presented.(68) The qualitative interviews captured a range of views from clinicians and other primary care staff involved in the study, which could be done in a relatively small sample because of the specificity of experiences.(68) It was possible to purposively sample for clinicians and non-clinicians from recruiting and non-recruiting practices, which captured a good range of views and experiences with respect to the trial. The primary care staff also described considerable variety in terms of the IT arrangements for practices, although it seems likely that this study does not capture the full range of variation in UK general practice IT arrangements.

The parent sample captured experiences from all three arms of the trial and a range of experience of child ear infections. It also captured a range of views from parents from medium to affluent neighbourhoods but did not capture views of parents from more deprived areas. While the experience of being involved in the trial is quite specific, which means a small sample can still provide information power, we recognise that the experiences of parents from deprived areas may be different and we do not know how well the experiences of our sample represent experiences of parents from these areas. If larger numbers of parents had been recruited to the trial, it would have been possible to conduct purposive sampling of parents and captured a greater range of experiences, particularly those from more deprived areas.

## Results in context of other research

There is strong evidence that children with AOMd benefit from immediate oral antibiotics,(12) but to our knowledge, there is an absence of evidence regarding clinical effectiveness and economic implications of immediate topical and delayed oral antibiotics for AOMd in children without grommets tubes. REST has a sister trial still running in the Netherlands called PLOTs investigating the role of a combined topical antibiotic and steroid preparation, also for children with AOMd without grommets (<https://www.trialregister.nl/trial/6535>). This study has yet to report. While the non-inferiority design and eligibility criteria are similar for PLOTS and REST, the studies are complementary with regards primary outcomes, offering the prospect of meta-analysis using REST results.

The number of children recruited too small for definitive comment, but we noted our sample was older (median age 5 years (IQR 2 to 7)) than the median age of 3 years (IQR 1 to 5) reported by Smith *et al* in an observational study investigating the natural history of AOMd in children presenting to UK primary care.(3) We also note the predominance of boys (62%) in our sample.

Thirty-eight percent of children’s parents fully adhered to treatment as prescribed. Sixty-six percent of children prescribed immediate (oral or topical) antibiotics started them within 24 hours of randomisation, compared with 50% in the delayed oral antibiotic group, suggesting delaying advice was having only marginal effects to modify parental behaviour.

The RCGP Research & Surveillance Centre's Weekly Returns Service (see <https://www.rcgp.org.uk/-/media/Files/CIRC/WeeklyReport_Summer_wk32_2020.ashx>) provides weekly notifications for Communicable and Respiratory Disease for England graphically. For AOM, markedly lower numbers were evident compared with the 5-year average. Over the period when REST was actively recruiting, numbers were reduced between a quarter and a half compared with other years. We therefore estimate that at least one quarter of the shortfall of recruited patients (compared with those projected) could accordingly be explained by this unusual drop in relevant infections.

## Implications

### AOMd research

The clinical and research communities should wait for the PLOTs study to report, and for any REST-PLOTS data syntheses to be completed before deciding if sufficient evidence is available to change the management of children with AOMd, and whether further research investigating the clinical and cost-effectiveness of immediate topical and delayed oral antibiotics for children with AOMd is necessary.

If this question remains unanswered, the NIHR and research community will need to consider if a further ‘REST’ type study is feasible. We remain convinced that the most efficient way to conduct this study would rely on a functioning electronic trial platform. Efforts should therefore be focused on establishing this facility, not just for this research question, but for the wider research community.

### Recommendations arising from lessons learned

These are grouped by those responsible for the following activities: site identification, site set up, site training, platform development, platform installation, troubleshooting, platform function monitoring and data management. Finally, there are two recommendations for national stakeholders, including DH&SC and NIHR.

#### The NIHR CRN

1. *CRNs should keep logs of which sites have been invited, when and how many times. These should be shared with study teams, in order to populate CONSORT flow diagrams and allow a description of the generalisability of the recruiting sites.*

#### Sponsors

1. *Sponsors should consider accepting electronic versions of delegation logs with e-signatures. These should be designed such that submission of incomplete logs/ CVs is not possible*
2. *With large distributed trials with many sites a robust electronic data management system to track documentation should be employed.*

#### Trial management teams

1. *Where online site training is used, studies should provide training via a website that provides automated reminders and notifies the Sponsor and study team when training is complete.*

#### Electronic study platform

##### Developers

1. *Use of electronic trial platforms should be used to harness the unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where the key ‘drop offs’ are in the recruitment process from presentation to consent*
2. *All necessary platform preparatory activities and required resources should be clearly defined, taking care not to under-estimate either*
3. *The skills needed to set up a trial platform, and to set up a trial are distinct and complementary. Ideally teams should be co-located to ensure platform specifications meet individual trial requirements*
4. *Platform software needs to be compatible with all practice software systems*
5. *Closer integration with EHR providers would prevent incompatible updates [NB. this could be obviated if national criteria were agreed or the trial platform was integral to the EHR].*

##### Installers

1. *Project teams need to work closely with EHR providers and CCGs from the study outset to agree the software deployment process and the validation criteria required [NB. this could be obviated if national criteria were agreed or the trial platform was integral to the EHR]*
2. *A pilot install incapable of being used for recruitment and therefore not a site agreement requirement) should be performed on one computer in each practice, tested, and left to run for a week, before installing software on to other machines*
3. *Where software re-installation is required, it must be done in a way which does not disrupt the work of the practice.*

##### Troubleshooters

1. *Electronic study platforms require teams dedicated to: (i) development; and (ii) troubleshooting.*
2. *Careful consideration should be given to who is responsible for troubleshooting – while it may seem obvious this is done by the trial team (since it involves interacting with sites), it requires awareness of platform function and may therefore be better provided by the platform development team.*

##### Function monitoring

1. *Electronic trial platforms would be best served by a dashboard function to monitor and log platform functionality in real-time, providing real-time alerts and diagnostics for reduced function, and logging functionality across time and space.*

##### Data management

1. *The format of the final dataset to be extracted from the study database should be pre-specified to ensure appropriate data format and avoid the submission of linked clinical and personal data.*

#### National stakeholders, including DH&SC and NIHR

1. *Research funders need to formally recognise the potential of electronic study platforms if they wish to put the NHS at the leading edge of pragmatic research globally, allowing the delivery of new, near-real-time generalisable knowledge, and providing unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where the key ‘drop offs’ are in the recruitment process from presentation to consent, that influence final study sample representativeness.*
2. *The NIHR and research funders should consider convening a meeting of national stakeholders to define a strategy for the development, implementation, and ongoing management of electronic study platform software.*

## Conclusions

We are unable to comment on treatment effects due to the insufficient number of participants recruited. We were also unable to establish the feasibility of running a platform supported pragmatic trial for AOMd in primary care. The late development and intermittent functioning of the TRANSFoRm platform within the SystmOne electronic health record system resulted in low recruitment, failure to reach the required sample size and inability to answer the main research question. Our experience has highlighted the technical issues which need to be overcome before electronic trial platform technology should be adopted in the primary care setting.

We have carefully documented our experience and presented clear recommendations in the hope they will be used by the DH&SC, NIHR and wider research community. The prize is rich and the opportunity clear: to lead the world in the delivery of pragmatic research that quickly and efficiently produces generalisable new knowledge to improve patient care. The current SARS-CoV-2 pandemic perfectly illustrates the need for, and value of, infrastructure ready to quickly respond to the changing health needs of the UK population.

# TRIAL MANAGEMENT GROUP AND AUTHORSHIP

Table 17 summarises the roles and responsibilities for the REST TMG and report writing contribution. The TMG agreed authorship based on the following principles: (i) authors meet criteria set out by the International Committee of Medical Journal Editors Recommendations; (ii) Chief Investigators joint lead authors; (iii) lead authors for other sections to be put 2nd, 3rd, 4th (in order of where their section appears); and (iv) remaining authors commenting on sections to be added in alphabetical order (surname).

***Table 17. TMG roles, responsibilities and contribution***

|  |  |  |
| --- | --- | --- |
| *Name and author position* | *TMG role* | *Responsibility* |
| *Chief investigators* |
| Alastair Hay (joint lead) | Leads | Overall responsibility for leading the TMG in the design, scientific integrity, delivery, safety and publication of the trial, on time and within budget. AH drafted abstract, scientific summary, challenges and recommendations, and discussion; and oversaw results. MM drafted plain English summary and oversaw introduction and methods. Both reviewed final draft. |
| Michael Moore (joint lead) |
| *Section leads*  |
| Vasa Curcin (final) | Co-investigator | TRANSFoRm platform design and development lead, wrote first draft of TRANSFoRm elements, reviewed final draft.  |
| Jodi Taylor | Senior BRTC Trial Manager | Responsible for Trial Manager and BRTC staff. Oversaw SH, KT and AS drafting methods, reviewed final draft. |
| Nicholas Turner | Trial Statistician | Oversight of clinical data collection, clinical data analysis. Drafted quantitative results, reviewed final draft.  |
| Sian Noble | Senior Health Economist | Oversight of HE data collection, HE data analysis and writing, reviewed the final draft. |
| Christie Cabral | Co-investigator | Design, conduct and reporting of qualitative study, reviewed final draft. |
| Jeremy Horwood | Lead qualitative researcher | Design, conduct and reporting of qualitative study, reviewed final draft. |
| Vibhore Prasad | Co-investigator | Trial design, Nottingham, East Midlands and East Coast recruitment, proof read and reviewed final draft. |
| *Other authors* |
| Brendan Delaney | Co-investigator | Trial design, TRANSFoRm functionality within REST, reviewed final draft. |
| Kathryn Curtis | Trial Manager | Day to day responsibility for trial management, helped draft methods. |
| Roger Damoiseaux | Collaborator | ZonMw funded PLOTS (sister) trial investigator, trial design, results interpretation, reviewed final draft. |
| Jesús Domínguez | Research fellow | Lead TRANFoRm developer. |
| Sue Harris | Trial Research Nurse | Clinical input to trial paperwork, parent follow up, helped draft methods. |
| Paul Little | Co-investigator | Trial design, results interpretation, reviewed final draft. |
| Andrew Lovering | Co-investigator | Trial design (microbiological elements), results interpretation, reviewed final draft. |
| Richard Morris | Senior Statistician | Senior statistical and methodology expertise, trial design, results interpretation, reviewed final draft. |
| Kate Rowley  | Trial Coordinator  | Trial coordination, helped draft methods. |
| Annie Sadoo | Trial Administrator | Trial administration, helped draft methods. |
| Anne Schilder | Co-investigator | Otolaryngology expertise, trial design, North London CRN recruitment, reviewed final draft. |
| Roderick Venekamp | Collaborator | ZonMw funded PLOTS (sister) trial investigator, trial design, results interpretation, reviewed final draft. |
| Scott Wilkes | Co-investigator | Trial design, North East and North West CRN recruitment. |

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## Trial steering and data monitoring committees

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## Data sharing

All data requests should be submitted to the corresponding author for consideration.  Access to anonymised data may be granted following review.

## Individuals

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## Disclaimer

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# APPENDICES

## Appendix 1a: Website links to study introduction and training videos

<https://vimeopro.com/healthandcarevideos/bms-rest-trial/video/289262737>; [http://bit.ly/rest\_trial\_training\_video\_1](https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fbit.ly%2Frest_trial_training_video_1&data=01%7C01%7Cvasa.curcin%40kcl.ac.uk%7C9a2d2ee205214a65057908d853d6d1b9%7C8370cf1416f34c16b83c724071654356%7C0&sdata=0L9foNxKDJBuGIbUezIBYiU10QWM6BgvFtWtWDHkq8U%3D&reserved=0" \t "_blank" \o "Original URL: http://bit.ly/rest_trial_training_video_1 Click or tap if you trust this link.); [http://bit.ly/rest\_trial\_training\_video\_2](https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fbit.ly%2Frest_trial_training_video_2&data=01%7C01%7Cvasa.curcin%40kcl.ac.uk%7C9a2d2ee205214a65057908d853d6d1b9%7C8370cf1416f34c16b83c724071654356%7C0&sdata=O6FVCfLReg4SuwU0f9t2Uj7%2FfWZbbp%2Bb7rdMZUW79Zo%3D&reserved=0" \t "_blank" \o "Original URL: http://bit.ly/rest_trial_training_video_2 Click or tap if you trust this link.); and [http://bit.ly/rest\_trial\_training\_video\_3](https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fbit.ly%2Frest_trial_training_video_3&data=01%7C01%7Cvasa.curcin%40kcl.ac.uk%7C9a2d2ee205214a65057908d853d6d1b9%7C8370cf1416f34c16b83c724071654356%7C0&sdata=WWHb0dO0ouRnF%2FAiNgCs0KGugAIPHRlzlSaKAm4Uy6U%3D&reserved=0" \t "_blank" \o "Original URL: http://bit.ly/rest_trial_training_video_3 Click or tap if you trust this link.).