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ANTIBIOTICS FOR LOWER RESPIRATORY TRACT INFECTION IN CHILDREN PRESENTING TO PRIMARY CARE

ARTIC PC

Research Project Protocol

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ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BNF	British National Formulary
CI	Chief Investigator
CRF	Case Report Form
CRP	C-Reactive Protein
CTU	Clinical Trial Unit
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMP	Data Management Plan
DSMC	Data and Safety Monitoring Committee
DVS	Data Verification Site
EQ-5D	EuroQoL-5D
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HDPE	High-density polyethylene
HRQL	Health-related quality of life
HUI	Health Utility Index
IB	Investigators Brochure
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
LRTI	Lower Respiratory Tract Infection
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimum inhibitory concentration (*i.e.* the lowest concentration of antimicrobial that will inhibit the visible growth of a micro-organism after overnight incubation)
mls	Millilitres, volume of antibiotic or placebo to be taken by the child
ISF	Investigator Site File
NRES	National Research Ethics Service
PC-CTU	Primary Care – Clinical Trials Unit
PE	Pulmonary Embolism
PI	Principal Investigator

PSC	Programme Steering Committee
PSS	Personal Social Service
QALY	Quality-Adjusted Life-Years
QoL	Quality of Life
QP	Qualified Person
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

1. OVERVIEW OF RESEARCH

1.1. Design

RCT nested in an observational study.

1.2. Setting

Primary care defined as first point of contact, this maybe a General Practice or a Hospital Children's Emergency Department.

1.3. Prior Literature

Cochrane/Medline searches identified no placebo-controlled trials of antibiotics for children with uncomplicated Lower Respiratory Tract Infection (LRTI).

1.4. Target population

Children 6 months to 12 years.

1.5. Inclusion Criteria

Acute uncomplicated LRTI (acute cough as the most prominent symptom and lower tract symptoms/signs (sputum/'rattly chest'/coarse rhonchi; breathless; pain), Parent/guardian willing and able to be contacted for follow up and complete symptom diary for up to 28 days.

1.6. Exclusion

Non-infective (e.g. reflux, Pulmonary Embolism (PE)) or croup (where viral aetiology is very likely). Those with clinically suspected pneumonia or very unwell and/or unwilling to be randomised will be invited to participate in an observational study collecting the same data.

1.7. Baseline measures

Structured history/examination; pulse oximetry; optional x-ray (for clinically undetected consolidation); and optional samples: swabs (for microbiology) and pinprick blood sample (for CRP and Full blood count). The x-ray will take place in a facility with suitably trained staff and safety measures local to the recruiting site with the site being responsible for the optional samples.

1.8. Measurement of costs/outcomes

Primary outcome: duration of moderately bad symptoms (from validated symptom diary). Secondary outcomes: symptom severity (days 2-4); duration of symptoms until very little problem; the development of new or worsening symptoms; complications. Health related quality of life will be measured by proxy methods in which The EuroQoL (EQ5DY) will be completed by patients or carers for age older than 7, children will complete the questionnaire separately too on days 0,1,3, 7, 14 21 and 28. Follow-up (at 1 month): measure lung function (if aged 6+).

Outcome parameters for observational study: development of new or worsening symptoms; complications, diagnosis of pneumonia based on chest X-ray.

1.9. Sample size

938 children are required (for alpha=0.01, 90% power, 80% follow-up) to detect a 3 day difference in the effect of antibiotics for the primary outcome among any one of 5 clinical subgroups (see below). We assume a subgroup represents at least 30% of the sample (our data suggests 30-65% for each of the key subgroups).

1.10. Subgroups

Our provisional approach is to the following subgroups but this will be finalized in the analysis plan, the decision being made blind to the intervention group.

- Sputum seen and/or heard by parents ('rattly chest') or by clinician on clinical examination
- History of fever
- Physician rating of being unwell
- Short of breath
- Chest signs (non-focal coarse crepitations/rhonchi/wheeze).

1.11. Analysis

Data will be available as anonymized to the study analysts. All study staff must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via usernames and passwords. Information will be kept on an encrypted drive and backed up on a daily basis. Should the password-protected computer be stolen or mislaid, data from the study will remain available via backups made and access to this data protected from external parties by placing the data on an encrypted drive.

Should secure access to data from the questionnaire software be compromised, a member of the study team will download available data from the website and immediately remove the survey and data.

Disseminated results will not contain any personal identifiable data of individual participants.

Cox proportional hazards models will provide estimates both overall and for subgroups and estimates of interaction with intervention by subgroup. In addition we will explore to what extent results from additional tests (bacteriology, biomarkers, abnormalities on chest-X rays, etc) are potential effect modifiers, and will explore differences between the purely observational data set and the trial data and other large observational cohorts.(1, 2) We will conduct economic evaluation alongside the clinical trial. Costs will take an NHS and personal social service (PSS) perspective (primary analysis) and societal perspective (secondary analysis). If the intervention is proved to be effective, we will estimate as the costs per symptomatic day prevented and the incremental costs per QALY gained. Cost effectiveness acceptability curves will also be produced to illustrate the uncertainty. Also we aim to develop a diagnostic model to detect pneumonia and assess to what extent additional tests have added diagnostic value. In addition we also analyse the prognostic value of patient characteristics to assess disease severity and identify high risk patients.

2. LAY SUMMARY

Although chest infections are one of the commonest infections managed in children seen in primary care, there have been no placebo controlled trials to show what effect antibiotics have - in contrast to adults where there is now good trial evidence to shows that for most people antibiotics do not work. The trouble with prescribing for most children is that antibiotics are being used too much which is causing the bacteria to become resistant, which is likely to lead in the future to serious infections for our children becoming untreatable from ‘superbugs’. Most children who see the doctor with a chest infection currently get antibiotics, and the groups of children that are even more likely to get antibiotic treatment at the moment are those who have one or more particular features - phlegm, fever, shortness of breath, or rattly noises heard in the chest when the doctor listens with the stethoscope. It is a real priority to show which groups of children that doctors prescribe for currently benefit and which do not, so that antibiotics can be targeted appropriately and the effectiveness of antibiotics can be conserved for future generations.

In the study more than 900 children with chest infections presenting in primary care will be allocated by random numbers to either get amoxicillin (an antibiotic) or not get amoxicillin for 1 week, and see whether antibiotics make any difference to symptom severity, or the duration of illness. All children will be given advice about using painkillers and will be followed up carefully during the next month. The study will be large enough to be able to show which, if any, groups of children that doctors currently prescribe for benefit from antibiotics (such as those with fever compared to those with no fever), and which groups do not. Parents and children who are happy to have further tests will have any, or all, of a pinprick blood sample taken, a swab of the throat taken and an X-ray done. This is to

see whether simple markers of inflammation and infection or the presence of bacteria, or any lung involvement seen on the X-ray can predict benefit from antibiotics.

3. BACKGROUND AND RATIONALE

Acute respiratory infections are among the commonest conditions managed in primary care. The Department of Health recognises that antibiotic resistance is an increasingly serious public health problem in England, Europe and the world with rising resistance rates for a range of antibiotics, and a clear relationship between primary care antibiotic prescribing (responsible for 80% of prescribing) and antibiotic resistance. (3, 4) The costs of resistance are also often not included in current estimates of cost-effectiveness. (4) Although consultations rates and antibiotic prescription rates for URTI or chest infections declined sharply in the late 1990s until the early 2000s (consultation rate 160/1000 for females; 120/1000 for males), (5) it is clear that antibiotic use is rising again and the volume of antibiotics prescribed has now exceeded the peak in the late 1990s (https://www.gov.uk/government/publications/resources-to-support-the-2012-european-antibiotic-awareness-day-in-england). (4) The Chief Medical Officer of England has recently warned of catastrophic dangers posed by the overuse of antibiotics, with a key proposed solution of the increased quality of decisions about prescribing our existing antibiotics.

Children have higher consultation rates for respiratory tract infections than adults, and even when antibiotic prescription was at its lowest most children labelled as having URTI or chest infection still were prescribed antibiotics. (6) Data from our current ongoing observational study among children confirms that at least 60% of children are prescribed antibiotics, which translates to 3 million prescriptions for antibiotics for cough in this age group (6, 7) or approximately 41 million pounds annually in direct consultation and dispensing costs, let alone the indirect costs incurred by 'medicalising' illness in the family and wider social networks. (8, 9)

Although trials among adults suggest modest benefit even among important clinical subgroups, (10-12) we are aware of no randomised placebo-controlled trials available to either support or dispute the common use of antibiotics in children with chest infections. A national research priority is to do clinical trials of medicines in children to ensure children are better represented in RCTs and that medicines for children are more evidence based. Because of the lack of evidence in children it is difficult for doctors to go against the rising tide of antibiotic use to reduce prescribing antibiotics for children. It may be that antibiotics in children also have limited benefit, however the differences in immunity and anatomy between adults and children prohibit simply applying evidence derived in adults to the management of children. (13) If reduction in antibiotic prescribing is to be achieved, one of the key issue for patients and clinicians is the difficulty of knowing whether the child presenting is an 'average' child: as with adults there is likely to be variation in pathophysiology and disease severity among children with acute cough. (10, 14-16) It is highly unlikely that antibiotics are never indicated in a child with acute cough but there is very limited evidence to support doctors in targeting antibiotics. Therefore it is not surprising that important prescribing decisions are made by doctors using traditional but non-evidence based clinical signs like sputum production, fever, chest signs and being

unwell as indications for antibiotic use. (17-21) The latter data in adults is supported by data in 430 children in our ongoing observational study of acute infective cough – the key driver for antibiotic prescription for examination is the presence of crepitations (present in 40% of children). Symptomatic predictors of prescribing include productive cough ('wet cough/rattly chest/sputum'), shortness of breath, audible wheeze and fever, which are present in between 30% and 65% of children presenting with chest infections, and this has not changed over the last 10 years since our previous trial which included 100 children. (9)

However, we think that a trial simply powered to estimate the average effect of antibiotics would provide unconvincing evidence to persuade doctors not to prescribe, as doctors tend to prescribe in the face of uncertainty, giving patents the 'benefit of the doubt', (22) and continue prescribing to particular subgroups according to their own ad hoc criteria. Thus it is necessary to study the heterogeneity of these children with acute cough and explore whether clinical and pathophysiological determinants identify subgroups where antibiotic treatment is or is not effective.
Another pivotal issue concerning antibiotic treatment of children is costs. The costs involved in children with acute bronchitis also differ from those in adults, for example because parents or care takers are also involved, with associated productivity losses, both in paid and unpaid work. The lack of evidence of benefit also means there are no clear estimates of the likely harms for clinicians and patients such as diarrhoea, fungal infections, skin rash and other allergic reactions. However, prescribing antibiotics has costs – the cost of antibiotics, of dispensing, and increased reconsultation due to medicalising self-limiting illness. (9, 23)There is also the major threat of antibiotic resistance - which is dominated by primary care prescribing of antibiotics. (24)

Thus in order to effectively make the arguments to reduce antibiotic overuse in children and targeting antimicrobial therapy in an evidence-based manner, a sufficiently powered clinical trial is needed, in which relevant measurements are taken along in the analyses on the effects of the intervention under study. A large adequately powered trial will not only have the benefit of for the first time assessing the overall average effect of antibiotics, but will also allow estimation of the benefit of antibiotics in *a priori* clinical subgroups (fever, sputum, rhonchi on clinical examination) and subgroups determined by results of additional measurements. (25, 26) On the assumption that the trial might demonstrate moderate benefit of antibiotic both overall and among subgroups, the potential benefits of the trial might include:

1. Reduced costs of prescribed antibiotics
2. Reduced medicalisation and fewer unnecessary medical consultations in future episodes of LRTI
3. Reduced risk of anti-microbial resistance

Improved quality of care by providing evidence based information to patients (parents) and reduced unwanted side effects in children. If on the other hand the trial did demonstrate effectiveness and cost-effectiveness in some subgroups but not others, and this was demonstrated to be cost-effective, then there is still likely to be considerable scope for better targeting of antibiotics, and limiting antibiotic use.

In addition to assessing effects of antibiotic treatment in children it is also highly relevant to be able to assess disease severity and risk for complications. Apart from improving indications for antibiotic treatment, heterogeneity of disease severity is also important because of monitoring and if needed referring patients and informing them and their caregivers. Both diagnostic studies to detect relevant severe disease, most importantly pneumonia, and assessing risks for complications incorporating standardised registration of patient characteristics and additional tests are lacking. Therefore we are aiming to also perform an observational study along the trial described above to develop prediction models that are both feasible in daily practice and could enhance detection of relevant infections in children that warrant special attention from primary care professionals.

3.1. Why is research needed now?

Antibiotics may be indicated in a child with acute cough but there is currently no evidence to support targeting antibiotics for common presentations. Therefore it is not surprising that prescribing decisions are made by doctors using traditional but non-evidence based clinical signs (e.g. sputum production, fever, chest signs, being unwell) as indications for antibiotic use. Among 430 children in our ongoing 3C PRIME (27) observational study of acute infective cough the key drivers for antibiotic prescription are: rhonchi on examination (among 40% of children), and symptoms of productive cough ('wet cough/rattly chest/sputum'), breathlessness, audible wheeze and fever, which are present in between 30% and 65% of children presenting with chest infections. A trial simply powered to estimate the average effect of antibiotics would provide unconvincing evidence to persuade doctors not to prescribe, as doctors tend to prescribe in the face of uncertainty and give patients the 'benefit of the doubt'. Thus it is necessary to study the heterogeneity of these children with acute cough and explore whether clinical and pathophysiological determinants identify subgroups where antibiotic treatment is or is not effective. The costs involved in children with acute bronchitis also differ from those in adults, because parents or care takers are also involved, with associated productivity losses, both in paid and unpaid work, and the enormous potential costs of future antibiotic resistance are often not included in estimates of cost effectiveness. (28)

Research is particularly needed now as antibiotic resistance is a major national and international priority and has been identified as one of the key public health threats of our time in high profile reports. The urgency of providing evidence now is also highlighted by the fact that primary care prescribing has been increasing again for several years, and clear evidence is needed to inform the more rational use of antibiotics in primary care, particularly for one of the commonest illnesses in children.

4. AIMS AND OBJECTIVES

Our aim is to provide evidence to inform the management of chest infections in children. The objectives are:

- To estimate the effectiveness of amoxicillin overall and in key clinical subgroups of children presenting with uncomplicated (non-pneumonic) lower respiratory tract infection in primary care.

- To estimate the cost-effectiveness of antibiotics overall and in key clinical subgroups of children presenting with uncomplicated lower respiratory tract infection in primary care.

- To explore the estimates of effectiveness according to key pathophysiological subgroups (the presence of bacterial pathogens; raised C reactive protein measurement or white cell count; the presence of clinically undetected consolidation on X ray; oximetry; lung function).

- To develop prediction models to detect pneumonia in children and children at risk for complications (abnormal course of disease, hospital referral)

5. RESEARCH PLAN

This is a randomised placebo controlled parallel group trial of amoxicillin or placebo for children presenting with chest infections in primary care. The trial is nested within an observational study where the same measures and outcomes will be collected.

As agreed with the funder, a pilot phase will be carried out to assess the feasibility of this trial during the initial 6-7 months of the study. This will only involve the lead centre (Southampton) and between 5 and 10 GP practices and District General Hospitals each recruiting between 6 and 8 patients. For the pilot phase, the target is to recruit 30 participants in each group with a minimum of 15 participants in each.

5.1. Health Technologies being assessed

Main phase: Amoxicillin 50mg/kg in divided doses for 7 days.

5.2. Target Population

Children with chest infections (acute lower respiratory tract infection)

5.3. Recruitment

Recruitment will take place in Primary care, since this is where the vast majority of those presenting with acute Lower Respiratory Tract (LRTI) are managed**.** Table 1 (Appendix D) shows the process for recruitment for those children presenting to their healthcare providerwith acute LRTI. Eligible patients

will be informed about the study by the consulting clinician or other staff at the General Medical Practice or Hospital, who will explain the study and provide the patient with a patient information leaflet.

Recruiting sites will be provided with promotional study materials such as posters, short version participant information leaflets and interest cards to display and/or hand out, allowing the patients an opportunity to find out more about the study and consider participation.

5.4. Inclusion criteria

Children between 6 months and twelve years old presenting with and acute lower respiratory infection (LRTI), defined as an acute cough as the predominant symptom, judged by the doctor or Nurse Practitioner to be infective in origin, lasting <21 days, and with other symptoms or signs localising to the lower tract (sputum). (2, 15, 16) These inclusion criteria are not only very similar to the clinical criteria used in daily practice to diagnose acute bronchitis (29) but are also among the drivers of prescribing from our ongoing observational studies in children. (30, 31). This would mean the inclusion of at least one other symptom suggesting infection (a systemic infection (fever, raised temperature), coryza, wheezing, sore throat, earache). Children with previously diagnosed asthma presenting with acute respiratory symptoms felt by their doctor to be due to an acute infection and in whom antibiotics are being considered are eligible for randomisation, with additional anti-asthma treatment (e.g. increased bronchodilators or corticosteroids) also provided according to clinical need as assessed by the treating clinician.

5.5. Exclusion criteria

Exclude if:

- The cough is judged by the clinician to have a non-infectious aetiology (e.g. hayfever or asthma where there is no clear infective precipitant) or almost certain viral aetiology (croup, where antibiotics are not commonly prescribed. This includes where exacerbations of asthma are the clear and prominent cause of the cough/bronchoconstriction;
- Suspected Bordetella pertussis;
- Severe tachypnoea as judged by the recruiting clinician
- immune-compromised;
- antibiotic use in previous 30 days;
- Children with asthma whose presentation is felt to be due to a non-infective asthma exacerbation and in whom antibiotics are not being considered eligible, nor children without a previous diagnosis of asthma in whom the presentation is suggestive of asthma rather than an infection (as per national asthma guidelines, e.g a less acute history, predominant wheeze, breathlessness, reduced peak expiratory flow rate, asthma risk factors).

For the trial but **not the observational study**– also exclude:

- Children with hypersensitivity to any of the penicillins should also be excluded or to any of the excipients (see section 6).
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to amoxicillin.
- Children who are on concomitant medication which, based on the clinical judgment of the clinician, may lead to clinically significant interaction with amoxicillin.
- Children with known severe renal failure, hepatic failure, infectious mononucleosis (active or within last two months), or phenylketonuria.
- Children currently taking any medications known to interact with amoxicillin (e.g. probenecid, sulfinpyrazone, methotrexate, mycophenolate, oral anticoagulants) or increase the risk of adverse reactions (e.g. allopurinol).
- If a sibling living in the same household is already enrolled on the trial taking project medication
- Suspected pneumonia based on clinical examination (oxygen saturation below 92% or focal rales) or being very severely ill as judged by the doctor.
- Children previously entered into the ARTIC PC trial.
- Children who have been involved in another medicinal trial within the last 90 days.
- The criteria for referral to hospital using the NICE Feverish Children Clinical Guideline 160 and NICE guideline on Sepsis in Children and Adults. (32)
- individuals with very severe, oral steroid-dependent asthma who may be at greater risk of serious infection .

The age range was chosen because the prevalence of chest infections and the use of antibiotics is high in this group, and the children are more likely to be homogeneous regarding body composition, pharmacology and aetiology of respiratory tract infections. Children younger than 6 months are more likely to have immature immune responses and signs of a severe infection are more likely to be non-specific, and older children between 12 and 18 are more comparable to adults than the school children regarding body composition.

5.6. Consent

The legal guardian of the child will be asked to consent to the study after they have considered a patient information leaflet about the study (approved by an NHS Multi-Centre ethics committee) and had sufficient time to consider participation and ask questions. For those children who are able to understand the study, they will also be asked to consider an age appropriate patient information leaflet and ask questions about participation before also signing an age appropriate assent form. If necessary, clinicians will see other patients in order to allow sufficient time for patients to read materials and formulate questions. All legal guardians will be asked, at the time of consent, to complete a 'consent to contact form' with a preferred method of contact for follow up at day 2 by study staff and to be able to be contacted if they have opted to an x-ray (see 5.11. Data Collection - Measurements and follow-up).

5.7. Intervention

Pilot phase: As in the main trial we will use amoxicillin. The pilot is to test the acceptability of taking a placebo and test the study paperwork for both parents and recruiting clinicians.

Main phase: Weight related dosing is likely to provide the best evidence of effectiveness, and the best evidence to convince prescribers of the lack of effectiveness of antibiotics, since the alternative, the current BNF guidance using fixed doses, has broad categories of dosing according to age, and doses are particularly low for children in the higher end of the age ranges.

General Practitioners will specify the number of Milliliters (mls) of syrup to be taken three times per day using medicine syringes, based on a weight measurement of the child in light clothing taken during the consultation. We anticipate the easiest way to operationalise the dosing and avoid errors is to provide doctors with dosing schedules according to deciles of weight. Amoxicillin is the first choice antibiotic in LRTI and with current levels of intermediate resistance should cover most organisms. (10) The rationale for the dose (Amoxicillin 50mg/kg/24 hours (in divided doses) is in line with guidance from the BNF for children, and is supported by a Monte Carlo simulation to reach a Minimal Inhibitory Concentration (MIC) of around 1.5 - to cover *H. influenzae* as well as intermediate resistant *Pneumococci* for 90% of the intended population. (10) We estimate that no fewer than 5 days above the MIC is needed to achieve bacterial eradication. However, a 7 day course is more in line with current practice and so has been chosen on pragmatic grounds to allow not only for poorer compliance, but also for greater acceptability to clinicians (similar consensus was required for the previous similar trial in adults):(10) it is imperative that the intervention, and hence the results of the trial, are seen by clinicians (and parents) as providing a rigorous test of antibiotics with a sufficient dose and duration to conclusively estimate effectiveness.

In both arms, parents of the children will have trial medication and also be allowed to use self-medication *ad libitum* (paracetamol or ibuprofen). All parents will be instructed to seek medical assistance again in the event that symptoms progress.

5.8. Randomisation

Parents and children who consent to the study and agree to randomization will receive either antibiotic or placebo. The clinician will dispense sequentially numbered pre-prepared randomised packs. The randomisation codes for antibiotic or placebo will be kept by the manufacturer and with a dedicated unblinding service. Unblinding can occur if requested by clinicians for clinical reasons – for example where adverse events occurred (e.g. anaphylaxis, admission to hospital with life threatening illness (e.g. septicaemia; meningitis; severe pneumonia requiring ICU admission) and death.)

5.9. Pilot phase

As agreed with the funder, an internal pilot phase will be carried out to assess the feasibility of this trial during the initial 6-7 months of the study. This will only involve the lead centre (Southampton) and between 5 and 10 GP practices and or Hospitals each recruiting between 6 and 8 patients. For the pilot phase, the target is to recruit 30 participants in each group with a minimum of 15 participants in each.

5.10. Observational study for those refusing randomisation

Some parents will decline randomisation, due either to concern about getting antibiotics or not getting antibiotics. The main concern for the trial data is that due to selection bias the trial may end up addressing the milder end of the clinical spectrum. Hence we propose, as in our adult trial, (10) that those not consenting to randomisation are offered participation in an observational study where the same outcomes are collected so that the characteristics and outcomes can be compared with trial participants. We have allowed for up to 30% additional parents being willing to undertake the observational trial.

Observational study to develop prediction models;
In all patients included in the trial and observational study we will analyse the relations between patient characteristics and results of additional tests and on the other side the presence of pneumonia and the occurrence of complications.

5.11. Data Collection - Measurements and follow-up

This study is a randomised clinical trial during which clinical assessment as well as additional measurements regarding aetiology and disease severity will be made and related to the effects of treatment. The recruiting clinician will complete a Case Report Form (CRF) of comorbidities, clinical signs and the severity of baseline symptoms reported by the patient (rating each symptom 'no problem', 'mild problem', a 'moderate problem', or 'severe problem'). (10) Co-morbidity and respiratory tract infections in the previous year will also be documented. The data will be entered onto a secure, password protected, study specific database hosted by the Clinical trials Unit (CTU) see 10.3. Data Recording and Record Keeping page 39.

In addition a capillary blood sample and a single sweep dual viral/bacterial throat swab will be taken (we will use the same technique which has proven both very acceptable and with high yields in the TARGET cohort), and pulse-oximetry will be performed. Sampling will be optional to maximise the generaliseability of the sample, but we envisage from our experience of the TARGET cohort and other studies a high level of acceptance of sampling (at least 80%). The key microbiology of interest is the bacteriology for the common bacterial pathogens since we are interested in exploring whether the presence of pathogens predicts response to antibiotics (funded in this application) but we will also analyse the viral samples. With consent we will store samples for future analysis in a UK approved and Registered Biobank.

In the first week after inclusion, a chest x-ray will also be performed among willing participants. The study team will contact them with an appointment for the x-ray in a hospital close to their home. A standard x-ray request form will be used by all sites that will be supported by a Standard Operating Procedure detailing the reporting mechanism required for the study. This SOP will include both the timelines for images to be taken and definitions of the commonly seen conditions and when the requesting clinician should be informed of the outcome of the imaging. Any out of pocket expenses for attending the x-ray will be reimbursed.

The parents will keep a diary of symptoms and daily activities (including days away from work of parents) for at least one week and after that as long as symptoms persist up to four weeks after inclusion. All patients will be followed at 1 month when medication bottles will be returned and the symptoms diaries collected, and among willing participants over 6 years of age a forced-expiratory volume test will be done before and after administration of Salbutamol. This will allow some exploration of whether there is any difference in effectiveness among those with evidence of reversible airways obstruction. Parents/ guardians will be asked to guess individual treatment assignments (amoxicillin, placebo or don't know) and provide reasons for guesses on day 2 when as part of the telephone follow up before any evidence or side effects.

5.12. Outcomes

Duration of symptoms

The primary outcome will be mean duration of symptoms rated less than moderately bad or worse recorded for up to 28 days until symptom settle in a validated daily diary. (10, 33) This outcome is chosen as the primary outcome it matches parental concerns about more severe symptoms. (34, 35) The diary has previously been validated and was shown to be sensitive to change in both adults and children, and internally reliable (Cronbach's alpha 0.75 i.e. in optimal range). (9, 33) We have confirmed this in a subsequent trial which included 100 children using the same entry criteria as the current study: the diary was easily completed by parents, and the child data confirmed internally reliability (Cronbach's alpha 0.87) and sensitivity to change (Standardised response mean 1.53). (9) The diary items record the severity of the following symptoms: cough, phlegm, shortness of breath, wheeze, blocked/runny/nose, disturbed sleep, feeling general unwell, fever, and interference with normal activities. Each symptom is scored from 0 to 6 (0=no problem, 1=very little problem, 2=slight problem, 3= moderately bad, 4=bad 5=very bad 6=as bad as it could be). We propose the period until all symptoms daily registered by the parent of the patient are rated at least moderately bad as used in previous studies on acute LRTI. (10) We will also document the time taken to resolve symptoms are reported as 'very little' or 'no problem'. (9)

Severity of symptoms

The rationale for choosing the severity in the first 2-4 days after seeing the doctor, is that this is the time when symptoms are the most severe, (9) the inflammation is at its worst and when antibiotics

might make a difference. The duration of minor symptoms on its own is of less concern to children and carers and the time for resolution of all symptoms will be documented.

Side effects

Diarrhoea, rash, or nausea are common side effects of treatment and will also be recorded in the daily diary. (10)

Quality of life

Preference based measurement of quality of life in young children is under-developed, especially for children under 5 years. Current validated instruments in young children such as CH9D and EQ-5D are for children aged above 7, while HUI 2 and HUI 3 are intended for children age 5 years and older. EQ-5D-Y version can be used for children 7 years old and parent proxy for age 4-7. No single validated preference based measurement of quality of life exists in the current literature which can be applied in our study population (age 6 months to <12 year old). After discussion, we have decided to use EQ-5D-Y version. The questionnaire will be completed by parents/carers proxy for all patients at days 0,1,7,14,21 and 28). For children younger than age 4, only EQ5D VAS will be used.

Return with new or worsening symptoms or complications

These outcomes will be documented based on a structured notes review, which we have shown to be feasible. This outcome was one of the more useful outcomes to demonstrate antibiotic effectiveness in a previous large trial in adults. (10)

5.13. Health care resource use

Information on resource usage will be collected for all participants through notes review at the end of the study (28 days) covering medication, primary care visit community services, A&E attendance, out-patient appointment together with a Case Report Form (CRF) in which detailed resource use on hospital will be collected. The CRF will include resource use for major adverse events (e.g. anaphylaxis, complications, hospital admission). This will be used to assess any use of NHS and social services (primary care visits, community services, hospital inpatient and outpatient visits and A&E attendances.) In addition parent/carer's time off work in taking care of children will be collected through parents' diary.

5.14. Cost-effectiveness

The economic analyses will be taken from the NHS and PSS perspective. All resource usage will be priced based on published information (BNF, National reference costs and PSSRU). Accumulated costs and QALYs will be calculated through area under the curve methods for each patients. Missing value will be imputed using multiple imputation approach. Generalised linear model will be used to estimates the differences in costs and QALYs between the study groups and adjusted baseline

difference. If the intervention is proved to be effective, incremental costs per symptomatic day prevented and cost per quality adjusted life year gained will be estimated. Cost effectiveness acceptability curves will also be produced to illustrate the uncertainty.

5.15. Sample size calculation

Pilot phase: there is no sample size calculation.

Main phase: An alpha of 0.01 is chosen to allow for 5 pre-specified subgroups, which occur in at least 30% of children based on our previous data (sputum (65%), fever (64%); generally unwell rated as a bad problem (30%); short of breath (36%) abnormal chest signs (crepitations: 43%). Previous consensus documented less than 2-3 days difference in symptoms rated moderately bad or worse is unlikely to be a sufficient reason to prescribe antibiotics, and 3 days should probably now be the minimum given the short and long term disadvantages of antibiotics, (9, 10) and in particular increased national and international concern over the danger of antibiotic resistance (https://www.gov.uk/government/publications/resources-to-support-the-2012-european-antibiotic-awareness-day-in-england; https://www.gov.uk/government/news/prime-minister-warns-of-global-threat-of-antibiotic-resistance). (3, 4) To detect a hazard ratio for the treatment interaction of 1.7 (see Appendix 2 to this protocol: equivalent to 3 days difference between a subgroup and the whole sample), for the smallest subgroup of interest (30% of the sample), using the equations of Schmoor et al requires 738 individuals for 80% power and 938 individuals for 90% power (assuming 80% follow-up). (36) The other (larger subgroups) will have greater power. To allow for some leeway in our assumptions we will aim to recruit at least 1000 children.

5.16. Feasibility

Taking into account a mean yearly incidence of acute LRTI in children between one and twelve years old presenting in primary care of around 50/1000 (6, 37) and a practice list size of 6000, 40 children per year would expect to present, and if 1 in 2 are approached (approximately 20 per annum), and that 50% of parents agree to the trial (10 per annum), around 100 participating practices could recruit the sample during one winter. Although these assumption are based on our previous trial in LRTI (which included 100 children) and for other trials of antibiotic strategies in children, (9, 38) it sensible to make conservative assumptions. We will therefore perform initial internal piloting in one centre (5-10 practices) during the first winter to refine study procedures and ensure our assumptions are reasonable, and propose to recruit a minimum of 30 practices in 4 centres, and perform the main recruitment in up to 2 winters. With 1 month follow-up and 5 months data cleaning, analysis and report writing the whole study will take 3 and a half years.

Organisational difficulties, fewer than expected eligible patients, discomfort about patients eligibility and intervention efficacy, and patients' treatment preferences have been prominent issues in many trials, and have been recently described. (39) Unearthing the key problems for recruiters is of central importance in the piloting phase and we anticipate that the issues will become apparent, as they have

in our previous studies, in the process of detailed and sensitive discussion/iteration between an experienced trial manager and the 20-30 recruiting clinicians who are likely to participate in piloting.

5.17. Role of funders

The funder will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit for publication.

5.18. Nested qualitative studies

AIMS

(1) Prior to the start of the study itself, a small student study will be undertaken to explore a range of parent (and child/patient) views to aid the design of study procedures, to help optimize the acceptability of procedures once the trial is operational.

(2) To explore a range of parent (and child/patient) views on study participation, seeking to understand positive and negative experiences from start to finish.

TIMING

(1) Will take place in months prior to the study commencement/randomization.
(2) Will take place once participants have been randomized and participated.

METHODS

Semi-structured in-depth interviews will be used, but will be flexible to permit parents to speak freely on topics they deem to be relevant to ensure key emerging issues are captured. A subtle realist approach will be employed throughout the project to help represent participants' views.

SAMPLE

A purposive sampling approach will be designed to elicit views of a range of parents (and children where appropriate) (including a mix of men and women/boys and girls).

1. 15-20 interviews is likely to be sufficient to gather detailed feedback on parent (children/patients) views to help design the trial procedures.
2. Between 15 and 30 interviews should be adequate to represent the views of a range of parents (children/patients) following participation. Additional interviews will be conducted if saturation has not been reached.

ANALYSIS

We will follow the stages of Braun and Clarke's thematic analysis, assisted by NVivo (QSR international Pty Ltd) computerized analysis software as necessary. Analysis will aim to identify themes to help fulfil aims 1 and 2 whilst remaining flexible and open to emerging findings.

QUALITY

Standard methodological strategies will be employed to help safeguard rigour and ensure we produce trustworthy, plausible, and relevant findings. These will include careful purposive sampling, a clear exposition of methods (including field notes, and audio recording of interviews and accurate transcription of interviews, regular discussion between the fieldworker and senior qualitative researcher (including double coding/discussion of codes). Negative case analysis will help to refine analysis/safeguard against premature completion and the researcher will be tutored in the importance of a 'reflexive' sensitivity to the relationship between the researcher and research process.

5.19 Discontinuation / withdrawal of participants from trial

Each participant has the right to discontinue their study medication or withdraw from the study at any time. In addition, the investigator may discontinue a participant's study medication or withdraw a participant from the study at any time if the investigator considers it necessary (e.g. the participant experiences an adverse drug reaction, the participant's parent or guardian withdraws consent, or the investigator considers that further participation in the study would not be appropriate due to the personal circumstances of the participant or the participant's parent or guardian).

DISCONTINUATION OF STUDY MEDICATION

Clinicians will be advised to discontinue a participant's study medication if he/she experiences an adverse drug reaction related to the study medication. In addition, clinicians will be advised to prescribe an appropriate non beta-lactam antibiotic if antibiotic treatment is indicated. Parents/guardians of participants whose study medication is discontinued will still be required to complete their study diaries and questionnaires and will still receive telephone follow-up calls unless they choose to withdraw consent for these.

WITHDRAWAL

Once a participant withdraws or is withdrawn from the study, no actions will be taken to obtain data other than to monitor adverse events (see section 7.3. Procedures for Recording Adverse Events). Consent to proceed with reviewing the medical notes will be specifically confirmed for participants withdrawn from the study.

5.20 Definition of end of trial

The end of the trial will be the date of the last medical notes review of the last trial participant.

5.21 Thank you to parents

As a token of our thanks for helping with the study and the time doing the diary we will provide a £10:00 High Street shopping voucher.

6. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

6.1. IMP Description

The following drugs are defined as investigational medicinal products (IMP) for this trial

IMP	Dosage form	Strength
Amoxicillin	Oral Suspension (Powder for reconstitution)	250mg/5ml
Placebo for Amoxicillin	Oral suspension (Powder for reconstitution)	N/A

Amoxicillin is a pale yellow powder for reconstitution as suspension. The Amoxicillin product used in this trial will be a product with UK marketing authorisation.

The matching placebo product is formulated with excipients commonly used for antibiotic suspensions. The placebo product will be identical in appearance as a pale yellow powder for reconstitution (see section on treatment blinding). The placebo is formulated with excipients commonly used for antibiotic suspensions.

Both Amoxicilin and placebo will be packed in identical bottles. Each pack of IMP will contain either 3 bottles of Amoxicillin or 3 bottles of placebo, and a unique medication number will be printed on each pack of IMP.

Pilatus Pharma Ltd will be responsible for Qualified Person (QP) release of the IMPs for this trial.

TREATMENT BLINDING

Participants, their parents/guardians, healthcare professionals at recruiting sites and all research study staff will remain blinded to treatment allocation throughout the trial.

Both Amoxicillin and placebo will be packed in identical bottles. Each pack of IMP will contain either 3 bottles of Amoxicillin or 3 bottles of placebo, and a unique medication number will be printed on each pack of IMP.

DOSING

Weight (kg)	Dose (for oral administration)	Duration
4.5 to <6.5	100mg (2ml) TDS	7 days
6.5 to <9	150mg (3ml) TDS	7 days
9 to <12	200mg (4ml) TDS	7 days
12 to <15	250mg (5ml) TDS	7 days
15 to <18	300mg (6ml) TDS	7 days
18 to <24	400mg (8ml) TDS	7 days
24 to <30	500mg (10ml) TDS	7 days
30 to <36	600mg (12ml) TDS	7 days
36 +	700mg (14ml) TDS	7 days

LABELLING

The labelling of medication will conform to Annex 13 EudraLex Volume 4, Guidelines to Good Manufacturing Practice and Article 14 of Directive 2001/20/EC.

Each medication pack label will be printed with a unique medication ID number to ensure Amoxicillin and placebo are indistinguishable, and thus maintain allocation concealment (see 4.8 for the randomisation process).

SUPPLY OF IMP

Each study site will be supplied by the sponsor with IMP.

ORDERING OF IMP

Study sites are responsible for notifying the trial manager when IMP stock is getting low. The trial manager is also responsible for monitoring IMP level at study sites.

DISPENSING

A unique medication number will be printed on each pack of IMP which corresponds to one of the 2 treatment arms. Investigator staff will randomise and dispense by selecting the next sequentially numbered IMP pack.

IMPs are to be dispensed only in accordance with the protocol.

6.2. Storage of IMP

IMPs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all IMPs should be stored according to the instructions specified on the drug labels. IMPs are to be kept in a dry place below 25°C. We have a study specific IMP handling Standard Operating Procedure (SOP) and associated storage risk assessment.

Participants/parents/guardian will be instructed to store the reconstituted suspension at 2°C-8°C in a refrigerator.

Temperature excursion

Sites will be asked to report all temperature excursions to the trial manager immediately:

DISPOSAL OF IMP

Disposal will be at site.

6.3. Compliance with Trial Treatment

Parents or guardians will be asked to record in their study diaries each dose of study medication given to the child. Children whose study diaries indicate that they received 11 or more doses (75) of trial medication from days 1 to 5 inclusive will be considered to be compliant with trial medication. All randomised trial participants will be included in the intention-to treat population.

6.4. Accountability of the Trial Treatment

The investigator or designee must maintain an accurate record of the shipment and dispensing of IMPs. Monitoring of drug accountability will be performed by the trial monitor during site visits and at the completion of the trial.

6.5. Concomitant Medication

Trial participants will be advised to continue their usual regular medications while taking part in the trial. Healthcare professionals will record data at baseline on antiviral medications prescribed to participants during their current LRTI episode. Trial participants will be advised to continue taking any antiviral medications prescribed before study entry.

Parents/guardians will be advised that they can give their children additional medications for their LRTI episode while they are in the trial. They will be asked to record these additional medications in the study diary from days 1 to 28.

Since our trial will be double-blinded, clinicians will treat trial participants who re-consult in whatever way they feel is clinically appropriate. We will advise clinicians to prescribe an appropriate non

betalactam antibiotic if they feel that antibiotic treatment is indicated in a trial participant who re-consults due to clinical deterioration within 28 days of trial entry.

We will also advise clinicians to prescribe any other medications to participants during the study period if they feel this to be clinically appropriate. A member of the research team will extract data from participants' medical notes on further antibiotics and other medications prescribed during the 28-day period after study entry.

6.6. Post-trial Treatment

Participants will only be asked to take their trial medication for seven days. After participants have finished taking their trial medication, they will receive usual clinical care.

7. SAFETY REPORTING

All adverse events, for patients randomised into the trial, should be reported from the time the parent or guardian signs the informed consent form until four weeks after randomisation. Depending on the nature of the event the reporting procedures below should be followed.

Any questions concerning adverse event reporting should be directed to the Study coordination centre in the first instance. A flowchart will be provided to aid in the reporting procedures.

Adverse events presenting to the participants GP or Hospital will be notified by the practitioner. In addition participants will carry a study card which highlights the need to notify their own doctor regarding adverse events. As a final check all participants will be asked to consent to a medical notes review which will take place after study recruitment at a time when any letters will have been returned from out-patient appointments. This enables us to be confident of detecting adverse events which have not been notified using the first two mechanisms.

Hospitalisations for elective treatment of a pre-existing condition do not need reporting as Serious Adverse Events (SAEs).

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. These will not be collected for this study.

Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation (i.e an overnight stay) or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

Amoxicillin is a licensed medicine whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment) an Adverse Event Report form will not be necessary. We will collect data on events such as severe reactions to the antibiotics such as anaphylaxis, severe allergy requiring steroid administration, emergency hospitalization for chest problems and severe Clostridium (antibiotic related diarrhoea).

Unexpected adverse reactions to beta-lactam antibiotics will be highly unlikely amongst trial participants, as the vast majority of children will have previously received beta-lactams to treat other infections. For non-serious adverse reactions to trial medication, the Chief Investigator or a designated alternative study clinician will assess the urgency with which the participant's treatment allocation should be unblinded.

7.1. Definitions

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

7.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

7.3. Procedures for Recording Adverse Events

The side effects of interest will be collected through the completion of the daily diary only.

7.4. Reporting Procedures for Serious Adverse Events

Appendix E contains a flowchart summarising the procedure for SAE reporting. Healthcare professionals will report SAEs to the ARTIC PC coordination centre within 24 hours of becoming aware of the event. A medically qualified individual will be responsible for assessing the relatedness of the SAE to trial medication . All SAEs will be reported using the SAE form either on line or by paper and reporting this to the ARTIC PC coordinating centre. The ARTIC PC coordinator will maintain dedicated report lines with answerphone and fax facilities to allow reporting of SAEs. The answerphone and fax will be checked regularly during office hours.

The Chief Investigator (CI) or their designated representative will be responsible for assessing the expectedness of SAEs reported as being related to trial medication. Assessment of expectedness will

be based on the Summary of Product Characteristics. Reporting procedures for Suspected Unexpected Serious Adverse Reactions (SUSARs) are described in section 7.6.

The CI or designated PI at each clinical site will supply any supplementary information as requested by the MHRA, REC or ARTIC PC coordination centre.

7.5. Expectedness

Expectedness will be determined according to the Summary of Product Characteristics.

7.6. SUSAR Reporting

All SUSARs will be reported by the CI delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current study.

7.7. Safety Monitoring Committee

The trial Data and Safety Monitoring Committee will be responsible for reviewing SAEs after each recruitment season. The main aims of this review are as follows:

• To ensure the safety of each patient in the trial;

• To pick up any trends, such as increases in unexpected events, and take appropriate action;

• To seek additional advice or information from investigators where required;

• To evaluate the risk of the trial continuing and take appropriate action where necessary;

• To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment.

7.8. Development Safety Update Reports

In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial, or on request, a safety report to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

7.9 Criteria for the termination of trial

The DSMC will review SAEs after each recruitment season and discuss these with the Study/Trial Steering Committee (S/TSC). The Data and Safety Monitoring Committee, TSC or Sponsor may advise on whether the trial should be terminated.

8. HEALTH ECONOMICS

The primary economic analysis will be taken from a societal perspective but will also include the NHS and Personal Social Services (PSS) perspective. For NHS and PSS costs, we will collect data on medication, primary care visits, hospital stays, outpatient appointments and A&E attendances. All the information including adverse events will be collected through notes review forms at the end of the trial 28 days and CRFs. For the societal perspective, we will collect out-of-pocket spending, and time off work for parents taking care of children through a short questionnaire at the end of the study. All itemised resource usage will be weighted by their corresponding unit costs based on published sources (BNF, PSSRU and NHS reference costs).

We will measure the quality of life based on parents/cares proxy from EQ5DY, and the Visual analogue scale (VAS) used as part of the EQ5DY. The EQ5DY will be included as well as PedsQL™ (Pediatric Quality of Life Inventory™) on the basis that it measures quality of life at a point in time, and will be used in conjunction with the clinical outcome measures at days (1,7,14,21,28). This is important for an acute condition, and EQ5D was very helpfully used in the GRACE studies in adults to document change over time (and did change significantly which suggests it is likely to be useful in this population too). We will take this opportunity to investigate the associations between the different methods, which will help inform the use of proxy methods to measure children's' quality of life.

We will conduct an economic evaluation alongside the clinical trial. Accumulated costs and QALYs for each individual will be calculated based on an "area under the curve" approach. The cost-effectiveness analysis will be measured as costs per symptomatic day prevented and the incremental cost per quality adjusted life year gained (QALY). Generalized linear models will be employed to investigate the cost difference between interventions adjusted for baseline characteristics and bootstrapping methods will be used to produce incremental cost-effectiveness ratios and confidence ellipses. Cost-effectiveness acceptability curves will also be produced to reflect the probability of the intervention will be cost-effective at different given willingness to pay value per QALY gained. The cost effectiveness of antibiotics will be estimated in each subgroup.

Provisionally we propose not proceeding to long term modelling at this stage unless the intervention can be shown to be effective. For longer term modelling, particular attention will be given to including the benefits of reduced antibiotic use. Links will be made with work in progress in the Department of

Health on the societal value of reduced antibiotic resistance and with work by the Office of Health Economics on the incentives required for new antibiotic production.

9. STATISTICS

9.1. Description of Statistical Methods

The pilot data will examine organisational difficulties, fewer than expected eligible patients, discomfort about patients eligibility and intervention efficacy, and patients' treatment preferences have been prominent issues in many trials, and have been recently described.(34) Unearthing the key problems for recruiters is of central importance in the piloting phase and we anticipate that the issues will become apparent, as they have in our previous studies, in the process of detailed and sensitive discussion/iteration between an experienced trial manager and the 20-30 recruiting clinicians who are likely to participate in piloting.

In addition Parents will be asked at 2 days and in the symptom diary into which trial arm they believe their child to have been randomised. We will calculate the proportion of parents who correctly guess the randomisation group at each time point. Assuming that parents have remained blind to allocation, we expect that this proportion will be no greater than might have been expected by chance (i.e. the 95% confidence interval will contain 50%).
Based on this we would then make any required adjustments to the recruitment procedures.

No interim analysis will be performed, and all analyses will be performed blind to group allocation using Stata version 13 (StataCorp). Subgroup analyses according to clinical signs and results of additional testing will be specified in advance and finalised blind to intervention group. Analysis of duration of symptoms will be performed using Cox proportional hazard models controlling for the severity of baseline symptoms with models controlling for any covariates. Kaplan Meier curves will be used to demonstrate the resolution of symptoms graphically. Analysis of symptom severity will use linear regression modelling, again controlling for the severity of baseline symptoms. Any evidence of a difference in benefit from antibiotics among the whole cohort will be assessed and also the key subgroups, and for each outcome also estimate an interaction term for each subgroup.

Our statistical analysis plan will be finalized after the internal pilot, prior to the main analysis being completed and by the Trial Steering Committee.

In addition the study team will explore to what extent results from additional tests (microbiological swabs, biomarkers, abnormalities on chest-X-rays, etc.) are potential effect modifiers, and differences between the purely observational data set and the trial data and our other large observational cohorts. (40, 41)

Since this data set will be one of the best characterised and most intensively investigated cohorts to date, a range of exploratory secondary analyses using logistic regression will provide additional useful

information: we will develop both diagnostic models (for bacterial infection, and for consolidation), and prognostic models (for children who have poorer outcome: non resolution of symptoms or the development of new symptoms or complications), and if appropriate develop clinical scores and estimate whether there is an interaction of such scores with treatment.

9.3. The Level of Statistical Significance

A 5% significance level will be used for testing effects in the whole cohort and a 1% significance level for the testing of subgroup interactions, as per the sample size calculation.

9.4. Procedure for Accounting for Missing, Unused, and Spurious Data

The primary analysis will be a complete case analysis and a secondary analysis will be carried out using imputation (by documenting the change in estimates for a range of assumptions about resolution of symptoms among those with missing data, and using multiple imputation as appropriate).

9.5. Inclusion in Analysis

The primary analysis will be a complete case analysis on an intention to treat basis (i.e. whether or not children complied with antibiotics. A per protocol analysis among children where more than 5 days (approximately 80%) of the medication was used will be performed.

10. DATA MANAGEMENT

10.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. Source documents will be comprised of the following:

• Case report forms (CRF) for baseline assessment, follow-up and study discontinuation (completed by researchers in consultation with participant or their healthcare professional)

• Medical records (from which medical history and previous and concurrent medication may be summarised into the CRF or entered directly into Research Online)

• Laboratory results

• Diaries (hard copies completed by parents/guardians/participants)

• Correspondence (provided by participants, their healthcare professional or researcher).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, assent and baseline contact information page, the participant will be referred to by the study participant number/code, not by name.

10.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

Raw study data will be protected as far as is possible by the release being made following all investigations described in this Protocol and the associated study Publication Policy and Data Management Plan. We shall make data available to the scientific community once the analysis described in the protocol is complete. Interested parties may contact the corresponding author (Professor Paul Little, p.little@soton.ac.uk) in order to discuss the data and when it will be available for release.

10.3. Data Recording and Record Keeping

Study data will be entered, or transferred, into Research Online (RO). Participants will only be identified by a study-specific participant number and/or code in the Research Online database. Documents containing participant identifiable information will be stored separately from other study documents and saved within a securely hosted database separate from Research Online.

Research Online is a software package designed to capture, manage and store clinical study data. Its usage enables compliance with Good Clinical Practice (GCP) and regulatory guidelines by offering differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, de-identification of protected health information and comprehensive auditing to record and monitor access and data changes.

Research Online databases and web servers are hosted in data centers that meet the highest available standards for security. The servers are actively monitored to prevent failure (including memory, storage, CPU usage and network connections). Backups of all data are made on a daily basis. Backups are stored in secured locations that are geographically dispersed. Back-ups will be stored one year.

All Data Management functions will be performed in accordance with CTU DM SOPs. A Data Management Plan (DMP) is in place for all CTU hosted trials, outlining in detail the study specific procedures to ensure that high quality data is produced for statistical analysis. The DMP is reviewed and signed by all applicable parties, including the Study Manager and the Trial Statistician, prior to the first patient being enrolled.

Clinical study data will be collected by the CTU in paper format, direct data capture, and also direct upload of study data from external data sources (laboratory test results). The final repository for all study data will be Research Online. All Study Data Documents (SDDs) in paper format are date

stamped upon receipt and tracked within a study management database. A full pre-entry review ensures that all pages have been received, subject identifiers are consistent and obvious errors/missing data are appropriately addressed prior to entry. All paper SDDs are entered by independent data entry staff into the clinical database.

Data validation for all data entered into the clinical database is achieved by programming study specific checks at point of entry, or by execution of SQL based queries. The Clinical Data Manager will review all discrepancies and generated output. If clarification from a research site is required, the query is added to a Data Verification Site (DVS) Report, and subsequently issued. The Clinical Data Manager oversees the tracking of DVS reports until they are resolved, and applies any updates to the clinical database.

Prior to database lock, dataset review is performed by the Clinical Data Manager and the Trial Statistician. All critical data items are 100% checked against original SDDs (and subsequent updates) to ensure accuracy, and an error rate is established across all fields to ensure a consistently accurate dataset.

At the conclusion of the study and after the database has been locked, all essential documents will be archived until 3 years after the youngest participant reaches 18 years old. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

11. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Healthcare professionals participating in our study will be asked to submit proof that they have completed GCP training, or be required to undertake GCP training (e.g. register for the online GCP course provided by the CRN team or attend local face to face training).

The Study Management Group (SMG) will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The SMG will be comprised of individuals responsible for the study's day to day management (e.g. the CI, study manager, statistician, data manager) and will meet regularly.

The Study Steering Committee (SSC) will be convened to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The SSC will consist of at least 5 members including the Chief Investigator, a co-investigator and an independent member.

An independent Data and Safety Monitoring Committee (DSMC) will review the accruing study data after each winter during the study recruitment period and assess whether there are any safety issues that should be brought to participants' attention or any reasons for the study not to continue. The DSMC will consist of an independent statistician and at least 2 independent members.

12. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the study/trial protocol which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the study; or

(b) the scientific value of the study.

In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed and, if appropriate, the Sponsor will report it to the REC, Regulatory Authority and the NHS host organisation within 7 calendar days.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the clinical study, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

13.5. Participant Confidentiality

The study staff will ensure that the participants' confidentiality is maintained. Other than on the contact information sheet, consent form and, if applicable, assent form, participants will be identified only by a participant ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

13.6. The blood and throat swab samples provided in ARTIC PC

The University of Southampton as the lead centre, and as being responsible for contracting, as the 'Suppliers' of the blood and throat swabs confirms that any 'Material' subject to The Human Tissue Act 2004 consent provisions has been obtained with full, informed consent of the donor for its use as detailed in the protocol for the Study, and as outlined in the current, approved version of the patient information sheet and consent form. If applicable, these documents will be provided in conjunction with this agreement. The laboratories, or Biobank, the 'Recipients', shall keep the Material secure at the Recipient's laboratory and ensure that access to the Material is restricted to the Recipient and authorised co-workers as detailed in the current ethically approved research ethics application form and protocol for the Study. In this agreement 'the Material' shall include any and all materials, documents and information that the Supplier may provide to the Recipient. All documents and information provided with the Materials, including patient data shall be considered confidential. The Recipient agrees not to transfer or distribute any part of the Material or any extracts, replications, summaries or derivatives thereof to any third part with the prior approval of the Supplier, Study sponsor and any relevant ethics committee. The Recipient will confirm that the disposal, where applicable, of any remaining Material will be carried out in line with local disposal policies relating to the disposal of human tissue and in accordance with The Human Tissue Act 2004.

14. FINANCE AND INSURANCE

14.1. Funding

The study is funded by a National Institute for Health Research Health Technology Assessment Programme: REF: 13/34/64.

14.2. Insurance

The University of Southampton has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment which is provided.

15. PUBLICATION POLICY

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by a National Institute for Health Research Health Technology Assessment Programme Ref: 13/34/64. The publication policy for this Grant will state the lead author(s) and co-authors for each manuscript. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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17. Appendix A: Protocol Change Control

Version	Date	Summary of Changes	Author
V1.0	30 September 2015		Kim Harman
V2.0	22 January 2016	Removal of Co-amoxyclav as antibiotic in pilot phase, amended timetable, amended QoL measures, addition of thank you to parent/child, clarity of in and exclusion criteria.	Kim Harman
V3.0	04 March 2016	Clarity re samples and the Human Tissue Act 2004.	Kim Harman
V4.0	22 April 2016	Inclusion of analysis of viral samples. Inclusion of potential to store, subject to consent, samples for future research.	Kim Harman
V4.1	10 May 2016	Correction of spelling in section 1.7	Kim Harman
V5.0	29 July 2016	Clarity over exclusion criteria and sub group analysis, and amending Health Economic tools	Kim Harman
V6.0	17 February 2017	Removing Dr Broekhuizen adding Dr Van den Bruel as a Protocol contributor. Adding an exclusion criteria of 'Suspected Bordetella pertussis' amending wording to allow recruitment in Children's Emergency Departments, clarity over statistical methods, adding in new PPI members and their roles.	Kim Harman
V6.1	06 March 2017	Removing 'Confidential' from the front of the Protocol	Kim Harman
V7.0	14 June 2017	The Protocol now includes the statement 'At the end of the analysis described in this Protocol we will share anonymised data with other researchers after consideration of a request in writing to the Chief Investigator. We shall make	Kim Harman

		data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs' in the section 10 Data management sub section 10.2 Access to data. The reference to the NICE sepsis guideline has been updated as this is now published, Ann van den Bruel has been removed as a collaborator and Reuben Ogollah added as Steering committee statistician.	

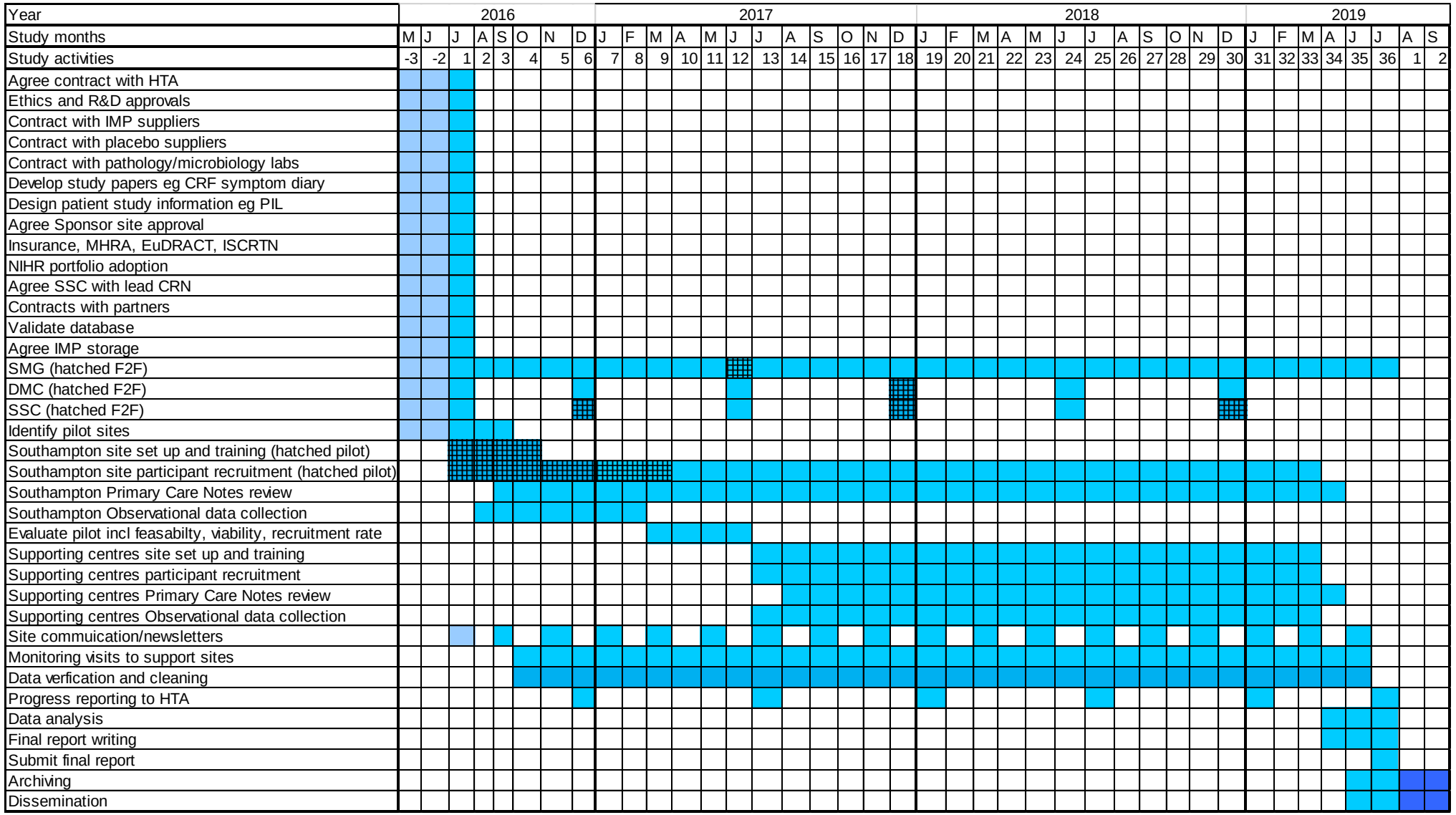
18. Appendix B. Power for interactions for the smallest clinical subgroup

(assuming 30% of the sample in the subgroup, for alpha=0.01 and assuming 80% follow-up); the proposed effect size is in bold

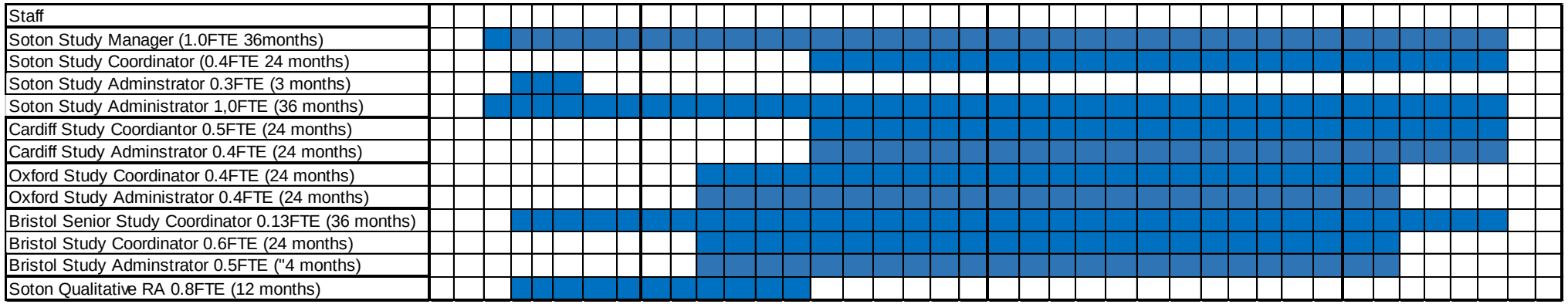
	80% power							
Interaction effect (days)		2	**3**	3.5	3.75			
Interaction Hazard ratio (HR)		1.4	**1.7**	1.9	2.0			
Total sample size		1808	**738**	509	442			
	90% power							
Interaction effect (days)		2	**3**	3.5	3.75			
Interaction HR		1.4	**1.7**	1.9	2.0			
Total sample size		2304	**938**	650	558			

19. Appendix C: TIMETABLE

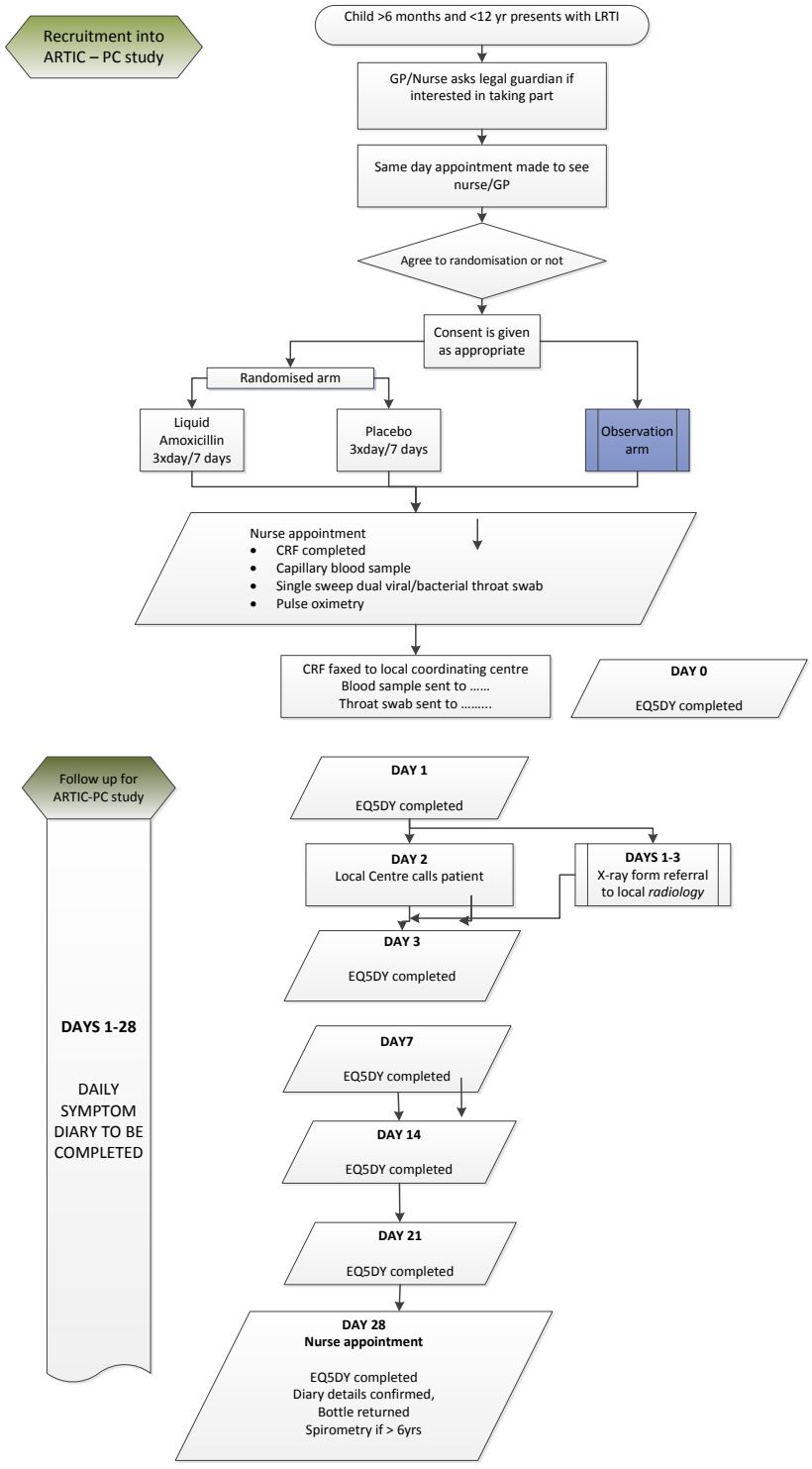
Study timetable



Staffing timetable


Staff
Soton Study Manager (1.0FTE 36months)
Soton Study Coordinator (0.4FTE 24 months)
Soton Study Adminstrator 0.3FTE (3 months)
Soton Study Administrator 1,0FTE (36 months)
Cardiff Study Coordiantor 0.5FTE (24 months)
Cardiff Study Adminstrator 0.4FTE (24 months)
Oxford Study Coordinator 0.4FTE (24 months)
Oxford Study Administrator 0.4FTE (24 months)
Bristol Senior Study Coordinator 0.13FTE (36 months)
Bristol Study Coordinator 0.6FTE (24 months)
Bristol Study Adminstrator 0.5FTE ("4 months)
Soton Qualitative RA 0.8FTE (12 months)

20. Appendix D. Table 1: Recruitment & baseline & FOLLOW UP process for ARTIC-PC



21. Appendix E. SAE Flow

SAE discovered at recruiting site or by ARTIC PC team member

↓

Initial SAE form completed and faxed, or completed, scanned and emailed or reported on the SAE form on the RO website **within 24 hours of being aware of the event**

↓

The CI or safety delegate will check the form for:

- Seriousness
- Relatedness
- Expectedness taking into account the reporting timeframe for the relevant competent authority

↓

The delegate will contact the reporting site if:

- If he agrees with the site and no further action is necessary
- Further information is necessary before an assessment can be made
- The event needs to be upgraded to a SAR or SUSAR

↓

- If no further action is required and the event is not a SUSAR then this is documented and all the information will be logged in the SAE database and any paperwork filed
- If further information is required this will be provided by the recruiting site

↓

- If the event is a SUSAR and
- Is fatal or life threatening it will be reported to the relevant competent local authority, REC, other bodies/parties according to local regulation/guidance **within 7 days** of the Sponsor or delegate becoming aware of the event
- Is not fatal or life threatening it will be reported to the relevant competent local authority, REC, other bodies/parties according to local regulation/guidance **within 15 days** of the Sponsor or delegate becoming aware of the event

↓

Once full SUSAR reporting has been completed all this will be documented and all the information logged in the SAE database and the paperwork filed