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Background

As you know all too well acute respiratory tract infections in children are commonly managed in Primary Care, we recognise many parents now do not always attend with this illness as we have suggested they do not need to be seen. To help overcome this we have

- made the inclusion criteria broad and
- produced posters that any pharmacy/dispensary adjacent to your surgery my display if they and you are willing to try this and see the potential recruits. This has been approved by the ethics committee. It is based on the one we provide for your waiting room.

The project is based on a pan European one for adults with the same baseline data collected and same optional samples (blood samples for CRP and FBC and throat swab for bacterial culture although we can now analyse for viral material at the same time and quantify the micro-organisms in far more accurate methodological process) and investigation (chest x-ray). This showed adults recover one day sooner in this predominately viral, self limiting, 3 week illness.

There is a lack of evidence to support GP's in targeting antibiotics in children with no evidence for different subgroups. We need to encourage all prescribers to include children that they might not normally consider for antibiotics on the basis that nationally clearly GPs are considering antibiotics for a broad range of children and we want to inform prescribing nationally and internationally.

If only the sickest children get in to the RCT and we show that antibiotics help we will have done everyone a disservice since this will not help us target antibiotics or enable us to advise GPs not to prescribe in subgroups of children.

Low prescribers are really not much more evidence based than high prescribers in this area (since there is virtually no evidence from trials in children) and we need to see if the common group of children who are prescribed antibiotics benefit and who do not benefit.

The question we are asking is on what basis would they give or deny antibiotics to a child that was coughing up productive sputum, had a fever, some SOB, or some coarse chest crepitations - this is an evidence free zone i.e. there is no evidence to help inform the decision, which is where ARTIC PC is trying to help.

We know

- Antibiotic resistance is increasing and yet Antibiotic use is increasing again.
- We felt this all together showed a need for a large study to examine the cost & effectiveness of antibiotic prescribing in children & to improve our quality of care for children by providing evidence based practice so made an application to the NIHR HTA to run

a randomised placebo controlled parallel group trial of amoxicillin or placebo for children with chest infections. The trial is nested within an observational study.

We have piloted now and now that clinicians can find the equipoise to randomise, parents will accept this and the paperwork is usable.

- The aim of the ARTIC PC study is to provide evidence to inform the management of chest infections in children. We wish to recruit 938 children + (to the trial only, the observational recruits are additional to this).
- The objectives of the ARTIC PC Study are to estimate:
    - Effectiveness of amoxicillin in children presenting with uncomplicated LRTI
    - Cost effectiveness of antibiotics

Effectiveness will be examined according to key pathophysiological subgroups (provisionally Sputum seen and/or heard by parents ('rattly chest') or by clinician on clinical examination, History of fever, Physician rating of being unwell, Chest signs (non-focal coarse crepitation's/rhonchi/wheeze)).

What is involved?

- A Child > 6 months & < 12 years (up to 13th birthday) presents with LRTI.
    - We are defining LRTI 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). These inclusion criteria are broad and not only very similar to the clinical criteria used in daily practice to diagnose acute bronchitis but are also among the drivers of prescribing from our ongoing observational studies in children.
    - 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.
    - Very broad and should make recruiting easy.

Exclusion criteria are

- Non-Infective cough (including non-infective asthma exacerbation),
- Immune compromised,
- Antibiotics in last 30 days,
- Penicillin allergy for the RCT.

Plus a list for those who should not be randomised. This will include

Hypersensitivity to any other beta lactam antibiotic

Jaundice/hepatic impairment due to amoxicillin

Medication known to interact with amoxicillin

Sibling enrolled in this project (to prevent inadvertent unblinding)

Previously enrolled in ARTIC PC

Severe tachypnoea (clinician judged)

Known Infectious mononucleosis

Known phenylketonuria

Children enrolled in another medical trial in the past 3 months

Meeting the criteria for referral to hospital using the NICE Feverish children clinical guideline CG160 and NICE guideline on Sepsis in Children and Adults NG51.

- Observational study & Randomised Controlled Trial are both explained & PIS provided, remember we have differing PIS sheets if you do not feel the child should be randomised because of e.g. suspected pneumonia, or has an allergy to penicillin and one for children to read. The observational study is essentially care as usual.
- Patient is screened for eligibility (GP or nurse practitioner, Nurse can screen) to ensure possible pneumonia is not randomised but these children can be consented to the observational study.
- If patient/carer are interested consent is obtained for either the observational study or the Drug trial (with blinded randomisation to Placebo or Amoxicillin). Remember consent can only be given by a parent or legal guardian unlike clinical care, we are happy for it to be received by any Healthcare professional. Assent can also be given if the parent/legal guardian or child wishes to do so. **Consents need initialling not ticking and signing by the recruiters and parent/legal guardian.**
- CRF 1 is completed (online or paper in the PID pack then transferred to the on line database ASAP)
- If the child is in the RCT complete and provide the unblinding card in the polypocket with the consent.

IMP care at site includes daily (Monday – Friday) temperature monitoring storing the IMP below 25 degrees in a secure location.

GCP in ARTIC

- Only the parent or legal guardian can give consent for a child, the child can give assent
- As Local Investigator (usually a GP but could be a pharmacist) can delegate duties but NOT responsibility with oversight of safety
- All staff involved need to understand the Protocol
- All staff involved need to recognise the use of the ISF
- Receive written informed consent (and record in the medical notes participation in the project)
- Complete the CRFs
- Recognise when things have gone wrong and report them early e.g. Protocol breach, SAE

The optional tests are decided by the clinician thinking it too distressing or child, by the parent / legal guardian deciding, or, if the child is old enough the child themselves

a. Blood sample (optional)
b. Throat swab (optional)
c. X-ray referral (optional) with reasonable out of pocket expenses paid by us.

We provide the consumables you will need. If however you wish to use traditional venepuncture for the blood collection then transfer to our microtainers please do so.

- Our primary outcome is via the Symptom diary so it is essential that you explain the importance of the diary and its completion to the parent/guardian (& give advice regarding storage of study medication if in RCT).
- Provide patient bag & present certificate and sticker.
- An appointment is made for 28days time (+/- 3 days).

CRF 1 at baseline

Includes:

- Inclusion/exclusion criteria
- Background information
- Symptom description
- Clinical examination (Temperature, HR, RR, O2 sats, Capillary refill)
- Medication advice

You can complete this on paper (in the PID pack and transfer to the on line database ASAP post recruitment) or directly on line. Our database is accessed via secure log on (we will provide individual log on details to recruiters on receipt of a work email address) via the web site https://www.researchonline.org/ which works best in Chrome a s web browser not Internet Explorer. Chrome is a free download.

We would like back at recruitment

A copy of the consent, a copy of the consent to contact (we follow up at day 2-3 to ensure happy with diary completion and if clinical concerns are raised encouraging return back to you), the confirmation forms in the PID pack for radiology, blood sample and throat swab. Please either post these in the freepost envelopes provided or fax to us on 023 8000 2380. This is to ensure you are paid for activity.

What is involved at the 28day follow up visit?

- Collect any unused study medication & estimate use - a pro forma is in the PID pack. Please destroy medicine this safely.
- Collect patient diary (if not returned and we will have reminded you if we have not had the diary back before this appointment) and post it back to us in one of your freepost envelopes.
- Peak Flow Expiratory Rate, and if possible Spirometry, (6years+ only), this is recorded on the on line database either immediately or onto paper (CRF 2 in the PID pack) and then transferred ASAP. This is for any child not just those with asthma.

What does the parent / legal guardian need to be willing to do?

Initial appointment will take about 30-40minutes

Parents/ legal guardians are being asked to consent their child into either a Clinical Trial or an Observational study

If they consent to the Clinical Trial then they will be asked to take the study medication (either Amoxicillin or placebo) 3 times a day for 7 days

Patient/Carer are being asked to complete a diary of daily & weekly questions from the first day they see you for 4 weeks or more likely until their symptoms have resolved, we know most of these illnesses last about three weeks

Patient/Carer to return for a 28day follow up appointment & return their diary & any unused study medication. Children >6years will also be asked to complete a peak flow test.

Randomising patients

- Recruiting clinician to dispense sequentially numbered pre-prepared randomised packs.
- Dispensing clinician will be blind to which group patients have been randomised to.
- Prepare the IMP – instructions and dosing information provided.
- Label the IMP (child's name and dose) box and bottles, explain if not making up all 3 bottles (as based on weight if small will not need 3).
- Unblinding only if requested by clinician for clinical reasons e.g. SUSAR.

Optional tests

Optional tests are optional but clearly we want as many as we can, if you try but fail still send us the confirmation form so we can pay for your time trying but do let us know so we do not chase up the results.

Remember to add 3 identifiers to the samples and requisition forms like any clinical sample plus the ARTIC PID

Remember to add your post code to the back of the box of blood containers or swabs

Blood tests

- Check did the parent/legal guardian initial the box for the (optional) blood test on the consent form?
- If agreeing to finger prick blood test apply Ametop early to let it work, do this test towards the end? Remember it may help the Ametop to work if you use cling film to keep the cream in place.
- You only need 0.5ml of blood for each test; CRP first – orange top
- Complete the blood requisition form in patient pack (remember to include the Patient Number) & send a copy to the study team for payment
- Complete the Lab blood requisition form in the box with the microtainers
- Complete the ARTIC sample form on the ARTIC PC online database
- Send both samples to the right lab via the sealable pack provided & remember to include a copy of the consent form with the bloods

Throat swabs

- Check did the parent/legal guardian initial the box for the (optional) throat swab on the consent form?
- Complete the swab requisition form in patient pack (remember to include the Patient Number) & send a copy to the study team (green top first and only purple top only if consent to store)
- Remember to complete the PID on the swab bottles (sticky labels provided)
- Complete the ARTIC PC online database form

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- Complete the pathology throat swab requisition form in patient pack (remember to include the Patient Number) Send sample(s) to the right lab via the sealable pack provided

Chest x-ray

Your local hospital will be expecting the requisition/report form and knows the children need seeing promptly as if they are on active treatment any infection will clear.

- Check did the parent/ legal guardian initial the box for the x-ray on the consent form?
- Complete an ARTIC PC requisition form for child x-ray and sent this to your hospital
- Send the confirmation of x-ray form to the centre for payment

It may help to reassure patents that the amount of radiation that a child is exposed to during the x-ray is equivalent to that received in 16hours of natural background radiation. Plus the cancer risk associated with this type of test is 1 in 800,000 this is extremely low especially when you compare it to the population child cancer rate which is 1 in 500.

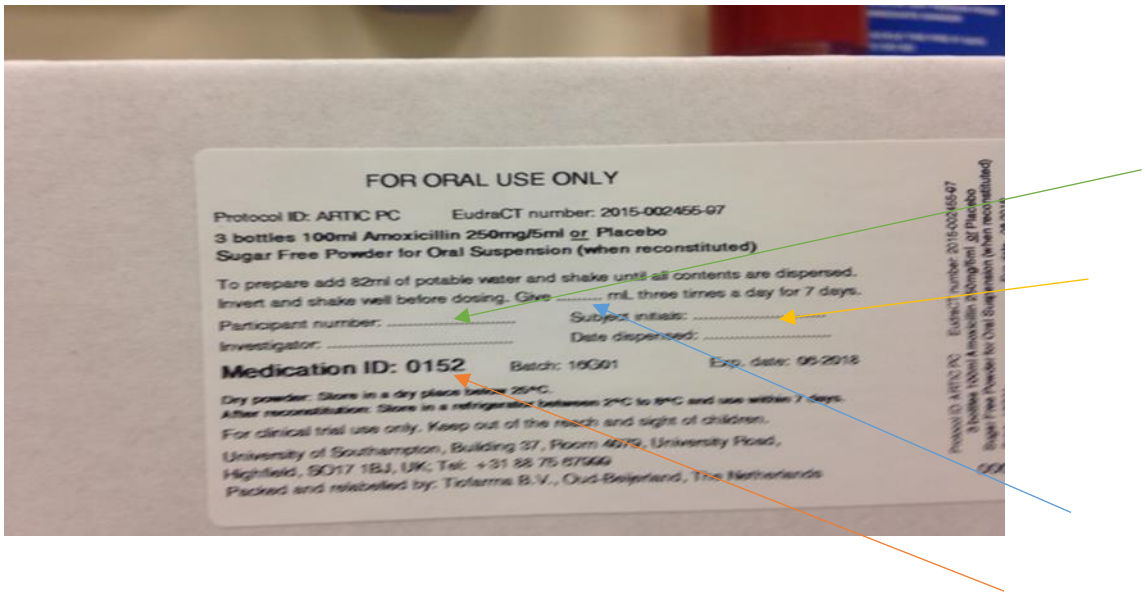
Study IMP

- Medication dosing to be titrated depending upon child's weight as taken at the initial visit – A dosing table is provided. We would prefer you to make up the medicines but please be sure to tell the parent you have done so.
- A nurse or HCA can give the medication to a recruit although you may want a 'counter signature' on the drug accountability form (this does not need to be a GP or nurse prescriber). Complete the accountability each and every time medication is dispensed.
- Advice to parents/guardians:
    - Medication to be stored in the fridge once it is made up
    - Medication to be taken 3 times a day for 7 days
    - They can also medicate with ibuprofen or Paracetamol
    - Seek medical assistance again of symptoms progress – normal safety netting advice

Unblinding is possible 24/7 but we would request if a child does return with worsening symptoms you do not unblind but prescribe a non beta lactam antibiotic. If you do wish to unblind have the recruits MID and PID available and ring 0031 88 75 67999.

Labelling IMP

To the outer box add the dose (blue), PID's initials (yellow), PID number (green) and note the MID (orange) for the CRF and medical notes.



To the bottles themselves add the dose (blue), PID's initials (yellow) and note the MID (orange).

How will you make best use of staff and time?

Consider triage to a recruiting GP or Nurse Practitioner involving reception too.

Double slots at the end of a clinical session

Nurse:GP shuttling model

Recruit during research slots which could be 'keep for days' in the winter months (releasing back for general appointments if they do not fill 1 ½ hours before? And possibly x2 a week?)

If only 1 GP / NP recruiting – sharing other workload with colleagues

SAEs

- SAE's will be collected from the point of recruitment until day 28
- SAE's include:
    - Anaphylaxis - severe allergy requiring steroid administration
    - Emergency hospitalisation for chest problems
    - Severe Clostridium requiring hospitalisation (antibiotic related diarrhoea)

Must be reported within 24hours of becoming aware of the event

Entered onto online database – preferred method

Or printed, signed as a true copy, & faxed to 023 8000 2380. If faxed please also phone Kim Harman 0778 6126108 to ensure SAE received

- Remember to also document it in the patient's medical records.

Withdrawal/Early Discontinuation

- Patients free to withdraw at any stage without giving a reason as in any research project.
- This should not be confused with patients who stop their study medication early or begin medication if in the study with no prescription. The baseline characteristics may be what we need to know to inform prescribing practice.
- Withdrawal form needs to be completed via the ARTIC PC database (we also provide hard copy)

Changes to staff or site activity

- We need to be aware of a change in PI and if this happens recruitment will need to be temporarily suspended until REC approves the new PI so tell us early if this is planned e.g. sabbatical or maternity leave and if you can provide a signed dated (current) CV early that will help make this a smoother process.
- Changes to staff may mean updating the
    - Signatory log
    - Training log
    - Delegation log so send us updated versions at any time. Provide us a work email and we will get a RO database password sent to the new staff member.
- Confirmation of IMP storage risk assessment if you change storage location.
- HRA confirmation/capacity to undertake the study and throughout the project if we make changes REC / HRA believe may impact your ability to deliver the project, we will provide the template email to send and ask if it is sent to the project manager and CI professor Paul Little.
- If you wish to close we need a delegated individual to sign the IMP back to us.

Internal research project documents

Your screening log helps us determine if our recruits are typical of the population so please do compete this as fully as you can. Thank you.

Your enrolment log will help you determine if we are paying for your activity (quarterly in arrears) and also when we contact you without us having NHS email addresses we cannot provide identifiable information so if we say recruit AB recruited on date xx/xx/xx dob xx/xx/xx you can see who that is.

Mistakes

Do happen do not worry but do own up quickly, Examples of Protocol deviations include

- Wrong age
- Sibling enrolled
- Prior enrolment

Please inform the study team as soon as you are aware of any Protocol deviations.

Payments to the site

We will ask you to become a supplier of the University as the regulations now prevent us paying you more than three invoices without this. To do this we will provide a new supplier form as an excel spreadsheet which is mainly a way of gathering the bank details to which the payment will be made. The good news is you only need to do this once then you are set up for any work you do for the University.

Payments for the NHS Service Support Costs are made by the uploading of the accrual to the national database so we need to keep that up to date every month. The payment is usually quarterly in arrears. There are two levels of reimbursement more being paid for the RCT recognising the additional time it takes to explain a RCT and randomisation including placebos and checking eligibility for safety.

The Research costs will be paid by the University of Southampton, we will send you an invoice to check and on place on headed paper and return it to us, again quarterly in arrears. Each activity has a cost associated with it and these have been considered with both who may be doing this and how long it is expected to take. **NB** the payment for site set up will be paid 50% at set up and in full when the first recruit is made, this may split over two quarters.

Maintaining your ISF

As ARTIC is a CTIMP (Controlled Trial of an Investigational Medicinal Product) it is governed by law. This means we have strict timelines in the reporting of SAEs (see your SAE SOP) and also

A recent CV signed and dated of Local Principal Investigator (in wet ink for your ISF)

ICH-GCP certificate from Local Principal Investigator (dated within 2 years)

CV signed and dated by ALL other team members (in wet ink in your ISF)

Completed and signed site agreement

Confirmation of IMP storage risk assessment which has been authorised by us

HRA confirmation/capacity to undertake the study

Signatory log with start/stop dates

Training log listing each item so 1,2,3 not 1-17

Delegation log listing each item so A, B, C not A-P with the PI authorising each staff member.

Please do contact us at any time with questions

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