ARCHIE clinical scenarios:
What to do if a child re-consults due to clinical deterioration

Scenario 1:
Child re-consults due to clinical deterioration after finishing study medication

Alfie was recruited into the ARCHIE study on day 3 of his flu-like illness. He took all 10 doses of his study medication. During this time his condition remained stable. However, two days after finishing his study medication, Alfie's parents notice that he has developed a cough productive of green sputum and his fever has got worse. Alfie's parents take him to the emergency department, where a doctor examines his chest, and notices coarse crackles in the left lower zone. The doctor diagnoses Alfie with pneumonia and prescribes him a course of amoxicillin in accordance with local prescribing guidelines.

Learning points:

- Clinicians may prescribe any antibiotic they feel to be clinically appropriate if an ARCHIE participant re-consults with a bacterial complication which they consider requires immediate antibiotic treatment.
- In these situations, our study protocol advises clinicians to consider treatment with a non beta-lactam antibiotic (i.e. an antibiotic which is neither a penicillin nor a cephalosporin) because the worst case scenario would be that the participant had deteriorated despite being randomised to the co-amoxiclav arm of the trial.
- However, clinicians may still prescribe a beta-lactam antibiotic if they feel that this is the most appropriate treatment for the child.
- Please note that, according to our study protocol, the child's treatment allocation would not be unblinded in this situation, since knowledge of whether the child received co-amoxiclav or placebo would not be necessary to inform the child's immediate clinical management.

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Scenario 2:
Child re-consults due to clinical deterioration while still taking study medication

Bella was recruited into the ARCHIE study on day 2 of her flu-like illness. After taking her study medication for 2 days, Bella develops worsening fever, pain in both ears, and bilateral otorrhoea. Bella's parents take her back to see her GP and ask for a prescription for co-amoxiclav as Bella was given this for a previous ear infection and it seemed to be effective. Bella's GP learns from her notes that a swab of Bella's ear discharge was sent to the laboratory when Bella previously had an ear infection, and that the infection was sensitive to co-amoxiclav, but resistant to amoxicillin and erythromycin. Bella's GP therefore prescribes co-amoxiclav and advises her parents to continue giving her the study medication until the course has been completed.

Learning points:

- Clinicians may still prescribe co-amoxiclav to ARCHIE participants who re-consult with bacterial complications before completing their course of study medication.
- In the ARCHIE study, children randomised to the co-amoxiclav arm will receive the standard dose of co-amoxiclav based on their age +/- weight. The British National Formulary states that the standard dose of co-amoxiclav can be doubled when treating severe infections. Therefore, in most cases, even if the child had been randomised to the co-amoxiclav arm of the trial, issuing a prescription for co-amoxiclav while the child is still taking their study medication is unlikely to be problematic.
- It would be advisable, however, to exercise caution in children with underlying conditions which may compromise the excretion or metabolism of co-amoxiclav (e.g. renal or hepatic impairment), and in children whose weight is less than 6kg (the lowest weight for which standard dosing instructions are available). In these children, an alternative antibiotic should be considered if antibiotic treatment is felt to be indicated.

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Scenario 3:
Child re-consults with clinical deterioration and suspected adverse reaction to study medication

Charlie was recruited into the ARCHIE study on day 2 of his flu-like illness. After taking two doses of study medication, he develops a worsening fever, sore throat and pain on swallowing. Charlie's parents are also concerned that his stools have become watery. They take Charlie back to his GP, who examines him and notes that he has swollen red tonsils covered in pus and tender cervical lymph nodes. Charlie's GP diagnoses him with tonsillitis. Charlie's GP also suspects that Charlie's watery stool may be an adverse reaction to his study medication. Charlie's GP advises his parents to stop giving him study medication. Instead, Charlie's GP prescribes a course of clarithromycin to treat his tonsillitis. Charlie's GP does not complete an adverse event report form, since diarrhoea is a known common side-effect associated with co-amoxiclav, and therefore does not require formal reporting according to the study protocol. Charlie's GP does, however, record that Charlie had diarrhoea on the week 1 follow-up form.

Learning points:

- Clinicians are advised to stop study medication in ARCHIE participants who re-consult with evidence of a suspected adverse reaction to study medication.
- The protocol advises clinicians to prescribe a non beta-lactam antibiotic to these participants if they feel that antibiotic treatment is still clinically indicated.