PediCAP Statistical Analysis Plan

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Revision History

Version	Author	Date	Reason for Revision
Draft 0.1	MC	29/10/2020	First draft – copy of protocol version 1.0
Draft 0.2	MC	15/01/2021	First substantial draft
Draft 0.3	MC	04/03/2021	Updated following comments from SW
Draft 0.4	MC	24/03/2021	Updated following comments from TMT
Draft 0.5	MC	14/04/2021	Updated following comments from TMG & SW
Draft 0.6	MC	04/05/2021	Updated following comments from MQ
Draft 0.7	MC	27/05/2021	Updated following review by TSC and DMC & final review of variables by MC
Draft 0.8	MC	01/06/2021	Updated following prior discussion with SW and MQ
Version 1.0	MC	02/06/2021	Upgraded to v1.0
Draft 1.1	MC	14/09/2023	Updated to protocol v3.0 and following DMC and SW suggestions
Draft 1.2	MC	02/10/2023	Updated following comments from SW
Draft 1.3	MC	12/10/2023	Updated following comments from Mike Sharland (CI) and MQ
Draft 1.4	MC	20/11/2023	Updated after comments from JB
Version 2.0	MC	28/11.2023	Upgraded to v2.0

Contents

Trial design

1.1. Design and outline

PediCAP is a multi-arm, open label randomised controlled trial of treatment strategies (drug and duration) for severe pneumonia in children.

The main trial (PediCAP-A) will recruit 1,100 children. A subset of 330 children will also be recruited into a microbiology substudy and an additional 120 children will be recruited into a PK substudy (PediCAP-B). This document refers to the efficacy and safety analyses for all children in PediCAP-A and PediCAP-B. Microbiological, pharmacological and health economic analyses will be covered elsewhere.

All children will initiate treatment with intravenous antibiotics as per the relevant site's standard of care within predefined regimens.

In the main trial (PediCAP-A), children will effectively firstly be randomised 5:5:1 to either oral step-down amoxicillin (amoxicillin group); oral step-down co-amoxiclav (co-amoxiclav group); or to remain on intravenous antibiotics (IV group). Within the amoxicillin and co-amoxiclav groups, children will simultaneously be further randomised 1:1:1:1:1 to receive 4, 5, 6, 7 or 8 days of total antibiotic treatment (from the start of intravenous antibiotic therapy). Children randomised to the IV group will receive 5 days of treatment with one of the PediCAP standard of care IV antibiotic regimens. Thus, each child in the main trial will be randomised to one of 11 different groups. Oral treatment will commence when the child is judged well enough to take oral antibiotics, which will be given with food where possible.

In the Phase II PK trial (PediCAP-B), a separate group of children will be randomised 1:1 to oral step-down with co-amoxiclav 4:1 vs 14:1 (1:1 randomisation ratio) for a total duration of 6 days antibiotics from the start of intravenous antibiotics.

Treatment will be open-label without blinding and will be dispensed at the point of oral step-down for the amoxicillin and co-amoxiclav groups, for the duration needed to complete the randomised total antibiotic course (starting at the time intravenous antibiotics were administered, excluding any antibiotics taking in the community prior to admission).

The trial design is summarised in the trial schema overleaf.

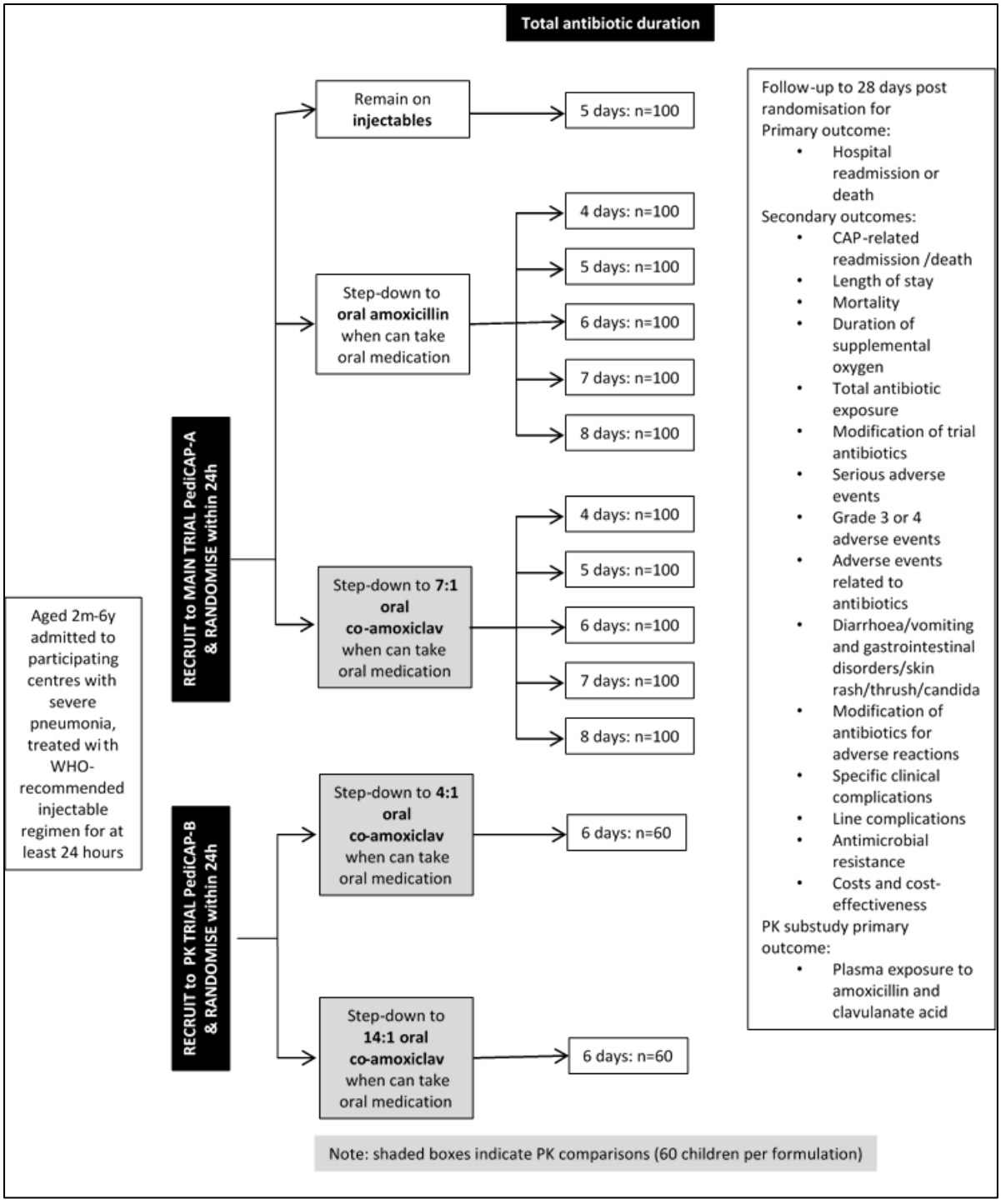

Figure 1: PediCAP trial schema

1.2. Trial population

Eligibility to the trial is based on the participant meeting all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

1. Aged 2 months to 6 years inclusive
2. Weighing >= 3kg and <30kg
3. Admitted to hospital with severe pneumonia judged to require at least 24h of intravenous antibiotics by the treating physician
4. Difficulty breathing (with or without cough reported by parent/carer) PLUS one or more of
    a. Central cyanosis or hypoxaemia (room air pulse oximetry <90%)
    b. Any sign of severe respiratory distress (e.g. severe chest indrawing, grunting, nasal flaring, head nodding)
    c. Signs of pneumonia (fast breathing (defined as respiratory rate ≥50 breaths per minute at age 2-11 months and ≥40 breaths per minute at age 1 years or older) or chest indrawing) PLUS a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions)

    occurring at any time from admission up to randomisation.
5. About to initiate or already initiated intravenous benzylpenicillin plus gentamicin, ampicillin plus gentamicin, benzylpenicillin or ampicillin alone, ceftriaxone alone or cefotaxime alone
6. Received at most 24h of these intravenous antibiotics at the point of randomisation (that is, first dose of any intravenous antibiotics must have been administered no more than 24h previously at randomisation)
7. Parent/carer willing to accept and adhere to all possible randomised allocations for their child (including 5 days of intravenous antibiotics if joining PediCAP-A) and signed written informed consent available from parent/carer
8. Available for follow up for the entire study period; specifically, parent/carer willing to return with their child to clinic at 4 weeks, and be contacted at minimum by telephone at weeks 1, 2 and 3

For children enrolled in PK or microbiology substudies, additional inclusion criteria are:

9. If undergoing additional PK sampling: willing to provide samples and potentially to stay in hospital for up to an additional 12h (separate consent will be obtained for PK sampling which may be refused and the child still join the main trial (PediCAP-A): consent for PK sampling is required for inclusion in the Phase II PK trial (PediCAP-B))
10. If undergoing additional microbiological sampling: willing to provide samples at enrolment, discharge and week 4 (separate consent will be obtained for microbiological sampling which may be refused and the child still join the main trial (PediCAP-A))

Exclusion criteria

1. Point-of-care semi-quantitative C-reactive protein (CRP) test < 10mg/l at screening (very unlikely to represent severe pneumonia requiring antibiotics)
2. Likely nosocomial pneumonia (onset >48h post-admission)
3. Admitted to hospital overnight in the last 28 days (possibility of nosocomially-acquired pneumonia)
4. Known or anticipated need for invasive ventilation or admission to intensive care
5. Clinician considers this episode to be predominantly due to reactive airways disease (e.g. asthma) (wheeze responsive to bronchodilators, see Manual of Operations (MOP) for more details)
6. Clinician considers this episode to be due to viral bronchiolitis alone in a child under 1 year

7. Documented penicillin allergy or contra-indications to penicillin/amoxicillin/co-amoxiclav
8. Anticipated need for systemic treatment with an antibiotic other than trial regimens during hospital admission or in the following 28 days (e.g. for *Pneumocystis jirovecii*)
9. On long-term antibiotics for prophylaxis or treatment (e.g. for tuberculosis treatment or cotrimoxazole prophylaxis for HIV infection)
10. Previously enrolled in PediCAP

The primary analysis population is intention-to-treat, including all randomised children, regardless of treatment received. However, in secondary analyses we will also use inverse-probability weighting methods to adjust for deviation from randomised strategy, both duration of antibiotic treatment and oral-stepdown.

1.3. Primary outcome

The primary outcome measure is:

- Re-admission to hospital or death within 28 days post-randomisation (all-cause)

1.4. Secondary outcomes

Efficacy/effectiveness secondary outcomes (assessed in all children) are:

- Proportion of children experiencing pneumonia-related readmission to hospital or pneumonia-related death within 28 days post-randomisation (pneumonia-relatedness adjudicated by the independent Endpoint Review Committee)
- Length of stay required during the index hospitalisation (days) (excluding any additional day remaining in hospital solely for the purpose of trial-related pharmacokinetic studies), and total days of stay in hospital up to 28 days
- Proportion of children dying within 28 days post-randomisation (all-cause mortality)
- Total days of supplemental oxygen during index hospitalisation
- Total days of antibiotic exposure during 28 days post-randomisation, including antibiotics received during the initial hospitalisation and antibiotics self-reported by parents/carers at follow up visits
- Proportion of children requiring modification of randomised antibiotics for any reason other than early stopping, or requiring a subsequent course of antibiotics for any reason up to 28 days (also considered as separate components)
- Proportion of children requiring modification of randomised antibiotics for inadequate response, or additional courses in the index hospitalisation for CAP relapse

Note that the Endpoint Review Committee adjudicated endpoint has been updated to pneumonia related, rather than CAP related as in the protocol, as the Endpoint Review Committee did not feel they could reliable distinguish between the initial CAP and any nosocomial infection acquired during the initial hospitalisation.

Safety secondary outcomes (assessed in all children) are the proportion of children:

- Experiencing SAEs, including hospital-acquired infections
- Experiencing grade 3 or 4 adverse events
- Experiencing antibiotic-related adverse events

- Experiencing key solicited events (reflecting common drug toxicities), specifically diarrhoea, vomiting and gastrointestinal disorders, skin rashes, thrush/candida
- Modifying antibiotics for antibiotic-related adverse events (i.e. toxicity)
- Experiencing specified clinical complications including sepsis, lung abscess, empyema
- Experiencing line complications (complications related to IV access)

Note that by definition a hospital-acquired infection prolongs hospitalisation so is an SAE following Section 7. Therefore, the SAE secondary endpoint will include all hospital-acquired infections.

All outcomes in this section are addressed in this SAP.

1.5. Other outcomes

Other outcomes include:

- Tolerability of and adherence to oral medication
- Self-reported (by the parent/carer) symptoms in the child at each follow up visit

Antimicrobial resistance outcomes are:

- Changes in nasopharyngeal carriage of antibiotic-resistant (e.g. penicillin non-susceptible, methicillin-resistant) Gram positive bacteria; assessed in a subset of children
- Changes in faecal carriage of extended spectrum beta-lactamases (ESBL)-producing Gram negative bacteria; assessed in a subset of children

Costs and cost-effectiveness will also be evaluated as will pharmacokinetics of amoxicillin and co-amoxiclav.

Antibiotic resistance, costs and PK are not addressed in this SAP.

1.6. Sample size calculation

1,000 children randomised 1:1 to oral step-down with amoxicillin vs co-amoxiclav provides >80% power to detect a 6% absolute reduction (corresponding to a 40% relative reduction) in 28-day re-admission or mortality (all-cause) from 15% (amoxicillin) to 9% (co-amoxiclav) assuming 5% lost-to-follow-up at 28-days post-randomisation (two-sided alpha=0.05).

Randomizing 500 children between 5 equidistant duration groups for amoxicillin and for co-amoxiclav is sufficient to estimate the duration response curve within a 5% error margin in >95% of simulations [1].

For comparison of the co-amoxiclav step-down with the 5-day intravenous groups, randomising 500 vs 100 children respectively provides 89% power to demonstrate non-inferiority based on a 10% non-inferiority margin for a 9% failure rate (two-sided alpha=0.05) (power is >80% for failure rates up to 12%). A 10% non-inferiority margin has been recommended by the United States (US) Food and Drug Administration (FDA) for adult bacterial CAP based on similar hypothesised event rates with and without antibiotics to those observed in children [2].

Therefore the total sample size for the main trial (PediCAP-A) is 1,100 (including the additional 5-day intravenous group). There is no formal adjustment for non-compliance because the trial is

pragmatic, designed to evaluate the impact of strategic approaches to antibiotic choice and duration. Rather, non-compliance is a separate secondary outcome (incorporating change from allocated antibiotic regimen for any reason) which will be analysed separately, and the results of the primary analysis interpreted conditional on this.

1.7. Method of randomisation

Randomisation is stratified by site (5 sites, each recruiting 220 children). This factor has been chosen because of practicality (see below) and because it has the potential to modify treatment effects (i.e. lead to interaction) due to variation in other clinical management across sites, meaning forcing balance across the randomised groups is most important for this factor. Sites also vary in local standard of care of their most commonly used backbone IV antibiotics allowed by the trial. All other factors should be balanced between groups by the randomisation. The other randomisation in the factorial design is also effectively a stratifier, and hence ensures balance for each randomisation with respect to the other – effectively each child is randomised to one of eleven groups (oral drug × duration (10 groups) plus continuous IV). If instead there were two separate randomisation lists for the oral drug and the total antibiotic duration, then by chance randomised groups for the former could be imbalanced with regard to the latter randomisation (and vice versa).

Randomisation lists for PediCAP-A were prepared by the delegated statistician using random permuted blocks of varying size 11 or 22 randomly allocated, stratified by site.

1.8. Estimands

The intervention is the randomised drug and randomised duration.

The patient population is children with severe bacterial pneumonia requiring treatment with IV antibiotics, presenting to hospital in five African hospitals, as defined by the inclusion and exclusion criteria.

The primary endpoint is re-admission to hospital or death within 28 days post-randomisation (all-cause). Secondary endpoints are defined above.

The population-level summary which provides a basis for comparison between treatment conditions is the risk difference.

Anticipated intercurrent events and associated strategy are:

- Loss to follow-up: is expected to be low. Multiple imputation will be used for the primary outcome if rates are above 5%.
- Deviation from randomised strategy: Inverse-probability weighting methods will be used to adjust for deviation from randomised strategy, both duration of antibiotic treatment and oral-stepdown.

1.9. COVID-19

PediCAP was designed before the COVID-19 pandemic and so there are no explicit mitigation strategies. Rate of positive COVID tests in trial participants and any resulting changes to treatment will be monitored and addressed in the analysis if necessary.

2. Derivation of data to be analysed

2.1. Time

For all analyses, time will be from time of randomisation. Unknown times will be assumed to be midday. Duration of treatment will be measured in half day increments.

2.2. Definition of baseline

Baseline values for all measurements will be those recorded at enrolment in the screening, baseline, randomisation and laboratory tests forms. For measurements taken multiple times at baseline (e.g. presence/absence of chest indrawing), the most extreme measurements before randomisation will be considered as baseline. The protocol specifies that chest x-rays up to and including 72h from admission will be classified as baseline. However, as time of x-ray is not available, x-rays on the date of randomisation, one day before randomisation and up to and including two days after the date of randomisation will be classified as baseline.

2.3. Definition of visit schedule

Trial contacts are scheduled as follows:

- Trial screening (day 0 or day 1): Screening information will be collected and point-of-care CRP test performed.
- Trial entry (day 1): Baseline information will be collected, and a face-to-face assessment will be made and randomisation performed.
- Daily until discharge: face-to-face assessment will be made.
- Day of discharge: face-to-face assessment and confirmation of contact details.
- Week 1 (day 8-10), 2 (day 15-17), & 3 (day 22-24): face-to-face assessment if in hospital or follow-up telephone call if discharged (or face-to-face if usual practice).
- Week 4 (day 27-34): face-to-face follow-up (in exceptional circumstances, this visit may be conducted by telephone if the child is unable to attend the clinic/hospital).
- Acute events: face-to-face assessment if child returns to the randomising site.

Data from scheduled visits falling outside of the visit windows will be considered part of the scheduled visit. Rates of scheduled visits outside of the windows will be monitored. Follow-up data from children still in hospital will be taken from the in-hospital data on the relevant day or preceding days, where appropriate.

2.4. Definition of treatment failure

Treatment failure is defined in section 1.3.
The date of treatment failure will be the date of first treatment failure.

An independent Endpoint Review Committee will adjudicate on the causes of death and of hospitalisation (to enable an unbiased assessment of the secondary outcome, pneumonia related readmission/death) and whether (without knowledge of actual randomisation) events were unlikely, possibly/probably or uncertainly to have been related to each intervention, were those affected to have received them. This will increase the objectivity of these assessments and increase consistency between sites.

2.5. Definition of lost to follow up

Follow up is only for 28 days post-randomisation, and therefore we anticipate a low rate of lost-to-follow up. We plan to telephone parents/carers after 1, 2 and 3 weeks post-randomisation (when

this occurs post-discharge) to ensure that contact is maintained before the face to face follow up at week 4.

For operational management at participating sites, a child will be classified as “lost-to-follow up” (meaning no further attempts at contact are made) only when three unsuccessful attempts have been made to contact the parent/carer following non-attendance at the face to face follow up in week 4, including telephone calls in the first instance, and then attempts to visit a child’s home (based on the location provided at enrolment). If a child is contacted after being classified as “lost-to-follow up”, the 28 day follow up form should be completed, regardless of the length of time it takes to re-establish contact with the family, in order to record the child’s vital status at the time of the missed week 4 follow-up.

Definition of censoring

Children lost to follow up will be censored on the date they were last known to be alive, from any available information source. Surviving children will be censored at d28 when applicable.

Free text

Free text fields in CRFs may be corrected for spelling and further categorised.

Standardisation of anthropometry

Weight, height and MUAC will be standardised for age and z-scores calculated using WHO Reference 2007 Charts. Outliers more than four standard deviations beyond the mean at each time point will be queried with the appropriate site and set to missing if not verified.

3. Statistical analysis

Information will be presented in tables and may also be presented graphically to aid interpretation.

Recruitment data will be presented as per standard CONSORT diagrams[3]. Baseline data tables will be presented overall. Post-baseline data tables will be presented aggregated in two ways – by drug (IV, co-amoxicillin 7:1, amoxicillin) and by duration (4, 5, 6, 7, 8, for patients randomised to co-amoxicillin 7:1 and amoxicillin only). P-values of associated statistical tests will be shown by drug, by drug excluding IV only (i.e. amoxicillin and co-amoxiclav arms) and by duration. Variables will also be presented by factorial randomisation or arm if there is difference between randomised groups of $p<0.05$, used as a flagging device for imbalance and expected for 1 in 20 characteristics by chance, with p-values from Kruskal Wallis tests of differences between means for numeric variables and chi-squared tests or Fisher's exact test if cell values are small for categorical variables. As per a DMC request two p-values will be provided for comparison between drugs: one comparing amoxicillin and co-amoxiclav randomised groups and the other comparing co-amoxiclav and IV only randomised groups.

Statistical tests will use 95% confidence intervals unless otherwise stated. Associated two-sided p-values will be produced but binary conclusions of significant/not significant will not be drawn. There will be no adjustment for multiple testing, although interpretation of results will take this into consideration.

All analyses will be included in the interim and final reports unless stated.

3.1. Recruitment

- Screened and enrolled n(% of screened)
- Screened but not enrolled: n; reasons not enrolled: all, including multiple per participant if indicated
- Eligibility: number and reasons for any participant randomised in error and excluded, or ineligible and included in the analysis
- Randomisation: number randomised to each arm
- Follow-up: number with status (death, readmitted to hospital, not readmitted to hospital) ascertained by day 28 post-randomisation

3.2. Baseline characteristics

The following baseline characteristics will be summarised by the specified statistics.

Demographics

- Site: n(%)
- Age (months): mean/median (IQR) [range] N
- Age: n(%) 2-11 months, 1+ years
- Sex: n(%) male, female
- Weight (kg), height (cm), MUAC (mm): mean/median (IQR) [range] N
- Weight band: n(%) 3-<6kg, 6-<10kg, 10-<14kg, 14-<20kg, 20-<25kg, 25-<35kg
- (in final report only) Weight for age, height for age, weight for height, MUAC z-score categories: n(%) <-3, -3-<-2, -2-<2, 2-<3, >3

Medical history

- HIV status: n(%) infected, exposed uninfected, uninfected, unknown
- COVID-19 status at baseline: n(%) positive, negative, not tested
- Asthma, chronic lung disease: n(%)
- Vaccinations PCV any, HIB, Pertussis, BGC: n(%) yes, no, unknown
- If PCV, PCT type: n(%) PCV7, PCV10, PVC13, PCV unknown, multiple PCV (specified)

Severe CAP signs from admission to randomisation

- Central cyanosis, hypoxemia, severe chest indrawing, grunting, nasal flaring, head nodding, fast breathing, chest indrawing, inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions, moderate/severe malnutrition: n(%)
- Inclusion criteria 4a, 4b, 4c satisfied: n(%)
- Number of inclusion criteria 4a, 4b, 4c satisfied: n(%) 1, 2, 3
- Number of hours between admission and point-of-care CRP test: mean/median (IQR) [range] N
- Point-of-care CRP category at screening: n(%) 10-40, 40-80, >80 mg/l
- Chest x-ray results up to and including 72h from admission: n(%) chest x-ray done, chest x-ray interpretable, chest x-ray suggestive of pneumonia, chest x-ray not suggestive of pneumonia
- On oxygen at baseline: n(%)

Parent/carer reported symptoms and signs

- Fever, cough, child's sleep disturbed by cough, breathing faster, eating/drinking less, skin rash, vomiting (including after cough), diarrhoea, bloody diarrhoea: n(%) not present, present not severe, severe/very bad
- Fever, cough, diarrhoea number of days of symptoms if present: mean/median (IQR) [range] N

3.3. Treatment summary

Treatment before randomisation

A summary of treatment prior to randomisation will be presented.

- Receiving antibiotics in the community before admission: n(%)
- Duration of antibiotic treatment in the community before admission (days): mean/median (IQR) [range] N
- Duration of antibiotic treatment in the community before admission, for those that received antibiotics (days): mean/median (IQR) [range] N
- Initial IV regimen: n(%) ampicillin alone, benzylpenicillin alone, ampicillin plus gentamicin, benzylpenicillin plus gentamicin, ceftriaxone alone, cefotaxime alone
- Initial IV regimen grouping: n(%) any penicillin (benzypenicillin or ampicillin) alone, any penicillin plus gentamicin, any third-generation cephalosporin
- Number of hours between first IV dose and randomisation: mean/median (IQR) [range] N

Treatment after randomisation

A summary of treatment following randomisation will be presented.

- Duration of initial IV regimen (days): mean/median (IQR) [range] N
- Total duration of initial antibiotic treatment (days): mean/median (IQR) [range] N
- Total duration of initial antibiotic treatment: n(%) 2+ days before randomised to, 1 day before randomised to, day randomised to, 1 day after randomised to, 2+ days after randomised to. (2+ will be expanded if >10% of children fall into category)
- Antibiotic duration exactly as randomised: n(%)
- Received antibiotics other than permitted initial IV regimen and oral antibiotic randomised to: n(%)
- Received antibiotics other than permitted initial IV regimens and oral antibiotic randomised to: n(%)
- Received AWaRe classification Access Watch Reserve antibiotics to d28: n(%)
- Highest AWaRe classification antibiotics received to d28: n(%) Access, Watch, Reserve
- Final IV antibiotic: n(%) benzylpenicillin plus gentamicin, ampicillin alone, ampicillin plus gentamicin, ceftriaxone alone, benzylpenicillin alone, cefotaxime alone, other (may be broken down further)
- Received any oral antibiotic: n(%)
- IV antibiotic treatment following oral antibiotic treatment: n(%)
- Total days of antibiotic exposure to day 28 post-randomisation: mean/median (IQR) [range] N
- Change of treatment strategy due to COVID-19: n(%)
- Received any of conmed category (Steroid/Bronchodilator, TB antibiotic, Antiretroviral, Antimalarial, Antiviral, Blood product, IV fluid, Supplement / Electrolyte replacement, Cough Syrup, Antihelminth, Diuretic / beta blocker, Antihistamine) to day 28: n(%)

A summary of oral trial treatment following randomisation will be presented for the amoxicillin 7:1 and amoxicillin arms only.

- Stepped down to trial oral drugs: n(%)
- Oral step-down day: n(%) 0, 1, 2, 3, 4, 5, 6, 7, 8, 9+ did not step-down
- Step-down within randomised total duration: n(%)
- Stepped down within two days from randomisation: n(%)
- Stepped-down to randomised drug and dose: n(%)
- Completion of randomised oral course: n(%)
- IV drugs after oral step-down: n(%)

3.4. Discharge & post-discharge

A summary of discharge and post-discharge information will be provided

- Discharged by d28: n(%)
- Discharge location: n(%), discharge home, transfer to another healthcare facility
- Used other healthcare post-discharge: n(%)
- Children experiencing acute events who were returned to randomising site post-discharge: n(%)

3.5. Description of follow-up

A summary of follow-up will be presented.

- Visit status at week 1, week 2, week 3, week 4 follow-up: n(%) visit done within randomised window, visit done outside randomised window, died before visit, unable to contact caregiver, caregiver refused, stopped participation early, other, awaiting data (interim analyses only)
- Type of visit week 1, week 2, week 3, week 4 follow-up: n(%) child in hospital, face-to-face, telephone, visit not done/awaiting data

3.6. Post-baseline test results & symptoms

A summary of symptoms will be presented. Follow-up data for children in hospital will be taken from the in hospital CRFs in the seven days to the relevant follow-up day.

- COVID-19 status post-baseline: n(%) positive, negative, not tested
- COVID-19 status at any time point: n(%) positive, negative, not tested
- (final report only) Signs and symptoms of severe CAP at oral step-down: n(%)
- (final report only) Signs and symptoms of severe CAP at discharge: n(%)

3.7. Primary outcome analysis

For interim analyses, primary outcome data will include all randomised children. Primary outcome Bayesian, time to event, imputation, inverse weighting, duration-response and subgroup analyses may not be presented in interim analyses depending on total sample sizes, loss to follow-up rates and compliance to randomisation. Randomised duration will be considered as a factor, except in duration-response analyses. Primary outcome interpretation will consider all analyses on the primary outcome.

Primary outcome components

- Primary outcome measured: n(%)
- Readmission to hospital or death: n(%)
- Primary endpoint component: n(%),readmission to hospital only, readmission to hospital and death, death only, no death or readmission to hospital
- Death or readmission to hospital time period (earliest if both): n(%), day 1-7, day 8-14, day 15-21, day 22-28, not died or been readmitted
- Location where event took place: n(%) initial hospital, other hospital, home, no readmission
- Stepped down before readmission or death: n(%)
- Stepped down before death: n(%)
- Deaths within 28 days post-randomisation (all-cause mortality): n(%)
- Death time in hours from randomisation for children who died: mean/median (IQR) [range] N
- Death time period: n(%), day 1-7, day 8-14, day 15-21, day 22-28, survived
- Reason no primary outcome: n(%): unable to contact caregiver, caregiver refused, child withdrawn, other

The primary outcome components table by duration will also be produced for each randomised oral trial drug (amoxicillin and co-amoxiclav) separately.

Primary outcome initial analysis

- The primary comparison between randomised groups will be conducted using binomial regression reported on the risk difference scale
- The primary analysis will include all randomised children
- The primary analysis will use generalised linear models with binomial errors and the logit link function. Results will be marginalised to report differences on the risk difference scale
- The primary analysis will adjust for the randomisation stratification factors (drug, duration and site)
- The analysis will first test for an interaction between drug and duration. If $p > 0.05$, results will report the factorial site, drug and duration effects. If $p < 0.05$, results will report the site effects and then each drug/duration effect separately
- Results will also be reported marginalised across sites on the risk-difference scale
- The primary comparisons will be superiority of co-amoxiclav over amoxicillin (95% CI, with unacceptable value of 0) and non-inferiority of co-amoxiclav and amoxicillin in comparison to IV (95% CI, with unacceptable value of -10)

- Results from models with/without the interaction term (depending on main analyses above) will also be reported as sensitivity analyses
- Interim analyses comparisons between each arm and IV, between different oral formulations, and between the minimum and maximum duration in each oral randomisation with p-values below 0.001 (Haybittle-Peto type rule [4]) will be referred to the DMC for stopping consideration

Primary outcome duration-response analyses

- Duration-response analyses will be conducted regardless of the results from the primary outcome analyses
- Duration-response curves will be estimated separately for oral amoxicillin and oral co-amoxiclav randomised groups using fractional polynomials to flexibly model the impact of duration on response following Quartagno et al 2018 [1]. A fp2 model will be fitted with automatic model selection based on a threshold p-value of 0.05 and at least a linear slope remaining. Centre will be included as a fixed effect as per the focal analysis.
- A combined model will test for an interaction between drug and duration. If $p > 0.05$, results will be from analyses without interaction terms. If $p < 0.05$, results will include interaction terms
- Duration-response curves will report estimates of both the absolute success rates for each duration and the difference between the longest duration and each shorter duration
- Duration-response analyses on imputed data will be conducted if lost to follow-up is > 5%
- Subgroup analysis, as specified for the focal analysis, will also be conducted by drug and by duration

Primary outcome subgroup analyses

- If there is no evidence of an interaction between drug and duration, a combined model will test whether there is evidence that these duration-response curves vary between co-amoxiclav and amoxicillin using main effects and interactions (i.e. subgroup effects), specifically the following key factors:
    - Site
    - Number of inclusion criteria 4a, 4b, 4c satisfied
    - On oxygen at baseline
    - Age (2-11 months vs 1+ years)
    - Sex
    - HIV infection and exposure
    - Malnutrition (assessed by weight-for-height Z-scores, according to the WHO Growth Standards, and pedal oedema/MUAC; if missing will be imputed using baseline eligibility criteria and numbers imputed recorded)
    - Initial IV regimen (penicillin alone vs penicillin plus gentamicin vs 3rd generation cephalosporin alone)
    - Prior oral/intramuscular antibiotics before hospitalisation for the index CAP episode
    - Baseline point-of-care CRP (semi-quantitative, 10-40 vs 40-80 vs >80 mg/l)

    - Chest x-ray features (abnormal vs normal vs uninterpretable vs not done based on any chest x-ray up to and including 72h from admission)
    - Weight band
    - Stepped-down within two days from randomisation in oral randomisation arms only. (Although this is not a baseline variable, children are expected to be on antibiotics for at least three days after randomisation and it is therefore appropriate to use this variable to capture those children with less severe illness).
- If there is evidence of an interaction between drug and duration, subgroup analyses will consider each drug separately
- Other analyses described above may be repeated to further analyse differences between subgroups

Primary outcome ACCEPT analysis

- Primary outcome main analysis will also be conducted in a Bayesian framework.
- Analysis will use generalised linear models with binomial errors and the logit link function
- Results will be reported on the risk difference scale
- Analysis will adjust for the randomisation stratification factors (drug, duration and site), unless significant interactions were found in the primary frequentist analysis where the associated interaction terms will also be fitted
- Following the sample size calculation, priors will be specified for the treatment difference between both amoxicillin and co-amoxiclav and IV and co-amoxiclav. Priors will be transformed to the logit scale for consistency with analyses
- The main priors will be non-informative priors. Informative priors may be added at a later date
- For the comparison between the two oral arms:
    - The amoxicillin arm prior on the logit scale will follow a Normal distribution with mean -1.734601 and standard deviation 1.6. On the natural scale, this corresponds to a median of 15%, mean of 23%, interquartile range of (6%, 34%), 95% of the distribution within (0.8%, 80%), with 4% of the distribution below 1%.
    - The prior for the difference between the amoxicillin and co-amoxicillin arms on the logit scale will follow a Normal distribution with mean -0.5790339 and standard deviation 2. On the natural scale, this corresponds to median differences between arms of -2%, mean 0%, interquartile range (-12%, 8%) and 95% of the distribution within (-48%, 58%).
- For the comparison between IV and amoxicillin/co-amoxicillin arms:
    - The IV arm prior on the logit scale will follow a Normal distribution with mean -2.313635 and standard deviation 1.3. On the natural scale, this corresponds to a median of 9%, mean of 14%, interquartile range of (4%, 20%), 95% of the distribution within (0.8%, 56%), with 4% of the distribution below 1%.
    - The prior for the difference between the IV and amoxicillin/co-amoxicillin arms on the logit scale will follow a Normal distribution with mean 0 and standard deviation 1.5. On the natural scale, this corresponds to median differences between arms of 0%, mean 5%, and interquartile range of (-4%, 11%) and 95% of the distribution within (-25%, 54%).

- Posterior probability curves will be created for each arm
- The posterior probability of each arm truly being better or worse than the IV arm by at least 0%, 5%, 10% or 15% under different prior assumptions will be calculated
- The posterior probability the co-amoxiclav arm truly better or worse than the amoxicillin arm by at least 0%, ±5%, ±10% or ±15% under different prior assumptions will be calculated
- The posterior probability of each duration truly being better than total duration of 8 days by at least 0%, ±5%, ±10% or ±15% under different prior assumptions will be calculated
- Any posterior probabilities greater than 90% will be referred to the DMC for stopping consideration
- Similar approaches will be used to compare durations analysed using both factorial and duration-response (mfp) analyses.

Primary outcome time-to-event analysis

- Cox regression will be used to analyse time to first of rehospitalisation or death and time to death alone
- Analysis will adjust for the randomisation stratification factors (drug, duration and site). The drug-duration interaction term will be included if detected in the main analysis

Primary outcome imputation

- If lost to follow-up is > 5%, multiple imputation with chained estimating equations will be used to impute outcomes
- If required, imputation will be done separately within each randomised group to allow for unknown interactions, and will be based on outcomes and main baseline characteristics

Primary outcome inverse weighting

- Inverse-probability weighting methods will be used to adjust for deviation from randomised strategy, both duration of antibiotic treatment and oral-stepdown, which is a more efficient and less biased approach than defining a per-protocol population [5]

3.8. Secondary efficacy analyses

Secondary efficacy outcome reporting

- CAP-related readmission to hospital or CAP-related death within 28 days post-randomisation: n(%)
- Length of stay required during the index hospitalisation (days) (excluding time in hospital only for PK study): mean/median (IQR) [range] N
- Total days of stay in hospital up to 28 days post-randomisation (excluding time in hospital only for PK study): mean/median (IQR) [range] N
- Deaths within 28 days post-randomisation (all-cause mortality; also included in primary analysis table above): n(%)
- Days of supplemental oxygen during index hospitalisation: mean/median (IQR) [range] N
- Days of any antibiotic exposure during 28 days post-randomisation: mean/median (IQR) [range] N
- Modification of randomised antibiotics for any reason other than early stopping, or requiring a subsequent course of antibiotics for any reason up to 28 days post-randomisation: n(%)
- Modification of randomised antibiotics for inadequate response, or additional courses in the index hospitalisation for CAP relapse: n(%)

Secondary efficacy outcome analyses

- Binary secondary efficacy outcome analyses will use binomial regression or Fisher's exact tests if binomial regression does not converge
- Continuous secondary efficacy outcome analyses will linear regression with Normal errors, unless gross departure from normality is observed, where Poisson regression (for counts only), transformation or quantile (median) regression will be used. Ranksum tests will be used if there is gross departure from normality that cannot be adequately addressed by data transformation
- All secondary efficacy analyses will adjust for the randomisation stratification factors (drug, duration and site)
- Analyses will first test for an interaction between drug and duration. If $p > 0.05$, results will report the factorial site, drug and duration effects. If $p < 0.05$, results will report the site effects and then each drug/duration effect separately
- Analyses performed on the primary outcome may also be performed on the secondary efficacy outcomes if deemed appropriate

3.9. Secondary safety analyses

Secondary safety reporting

AE/SAE rates will be presented overall and split by body system, and displayed as n(%)M where M is the number of events experienced for all children experiencing at least one event (M>n).

- SAEs, including hospital-acquired infections: n(%)M
- Grade 3 or 4 AEs: n(%)M
- Antibiotic-related AEs: n(%)M
- Key solicited events (reflecting common drug toxicities):

    - Diarrhoea: n(%)
    - Vomiting and gastrointestinal disorders: n(%)
    - Skin rashes: n(%)
    - Thrush/candida: n(%)
- Modifying antibiotics for antibiotic-related AEs (i.e. toxicity): n(%)
- Experiencing specified clinical complications including:
    - Sepsis: n(%)
    - Lung abscess: n(%)
    - Empyema: n(%)
- Experiencing line complications (complications related to IV access): n(%)
- Key solicited events (above) by weight-band: n(%)

Secondary safety analyses

- Secondary safety outcome analyses will use exact tests and binomial regression for binary outcomes
- For AEs and SAEs, incidence rate ratios and their 95% CIs will also be estimated to allow for the possibility of multiple events occurring to the same infant. The data distribution of the AEs and SAEs will be examined and Poisson, negative binomial or zero-inflated regression will be used to estimate the rate ratios as appropriate, depending on the number of zero counts and the amount of over dispersion

3.10. Other outcome analyses

Tolerability of and adherence to oral medication

A summary of tolerability of oral medication will be presented for those in the oral amoxicillin and co-amoxiclav arms only.

- Problems taking tablets in the morning, evening, with number of tablets, size of tablets, swallowing tablets, taste of tablets, vomiting/spitting out of tablets: n(%) yes, no, NA
- (final report only) Carer problems dissolving tablets in liquid: n(%) a lot, quite a lot, not much, not at all, NA
- (final report only) Tablets dissolved in: n(%) tap water, milk, fruit juice, soft drink, other, NA
- (final report only) If tablets taken post-discharge, how much giving antibiotics interfered with carers daily life: n(%) a lot, quite a lot, not much, not at all, NA

Symptom diary of self-reported (by the parent/carer) symptoms in the child at each follow up visit

A summary of symptoms will be presented. Follow-up data for children in hospital will be taken from the in hospital CRFs in the seven days to the relevant follow-up day.

- Diarrhoea days in all children at each follow-up, n(%) 0, 1, 2, 3, 4, 5, 6, 7, missing information, awaiting data (interim analyses only)
- Diarrhoea days in discharged children at each follow-up, n(%) 0, 1, 2, 3, 4, 5, 6, 7, missing information, not discharged, awaiting data (interim analyses only)
- Bloody diarrhoea in all children at each follow up: n(%) no, yes
- Bloody diarrhoea in discharged children at each follow up: n(%) no, yes, not discharged

- (final report only) For all children at each follow-up: Parent-reported at each follow-up fever, cough, sleep disturbed by cough, breathing faster, eating/drinking less, skin rash, vomiting (including after cough), thrush: n(%) no, yes, not known
- (final report only) For discharged children at each follow-up: Parent-reported at each follow-up fever, cough, child's sleep disturbed by cough, breathing faster, eating/drinking less, skin rash, vomiting (including after cough), thrush: n/N(%) no, yes, not discharged, not known

3.11. Children in co-amoxiclav 4:1 & 14:1 arms

Secondary safety analyses for children randomised to co-amoxiclav 4:1 and 14:1 will performed in a similar manner to the main trial. The primary comparison of pharmacokinetics in the PK substudy children will be addressed in a separate SAP.

4. References

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