CAP-IT

Efficacy, safety and impact on antimicrobial resistance of duration and dose of amoxicillin treatment for young children with Community-Acquired Pneumonia (CAP): a randomised controlled trial

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STATISTICAL ANALYSIS PLAN

Version 2.0, 2-Dec-2020

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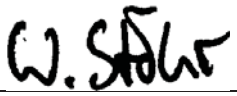
Wolfgang Stöhr	Trial Statistician		3. Dec 2020
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Revision History

Version	Author	Date	Reason for Revision
0.1	D Dunn, W Stöhr	12-Aug-2016	As in protocol version 2.0 (version in use when trial opened)
0.2	W Stöhr	13-Dec-2017	Initial full draft
0.3	W Stöhr	19-Dec-2017	Reviewed by D Dunn
0.4	W Stöhr	05-Jan-2018	Reviewed by D Gibb
0.5	W Stöhr	30-Jan-2018	Discussions with IDMC and TSC
0.6	W Stöhr	12-Dec-2018	Adapted to protocol version 4.0; add details for microbiology analysis
0.7	W Stöhr	14-Dec-2018	Reviewed by D Dunn
0.8	W Stöhr	2-Jan-2019	Reviewed by D Dunn. Sent to IDMC for comment
0.9	W Stöhr	18-Jan-2019	D Dunn responses/edits to comments from S Cousens (statistician on IDMC) statistician plus some structural changes
0.10	D Dunn, W Stöhr	28-Feb-2019	Responses edits to comments from D Gibb, M Sharland, J Bielicki
0.11	D Dunn, W Stöhr	22-Mar-2019	Changes to section 4.6.5.
0.12	D Dunn, W Stöhr	03-Apr-2019	Minor corrections
0.13	D Dunn, W Stöhr	09-May-2019	Changes to section 4.10 to match methods used by Bristol lab
1.0	D Dunn, W Stöhr	16-May-2019	Accepting of all suggested changes in version 0.13.
1.1	D Dunn, W Stöhr	31-July-2019	Clarification of sensitivity analyses in section 4.6.4 Adding a sensitivity analysis to 4.7
1.2	D Dunn, W Stöhr	21-Nov-2019	Minor changes or additions to 3, 4.7, 4.9 & 4.10.
1.3	D Dunn, W Stöhr	26-May-2020	Changes to section 4.10 to match methods used by Antwerp lab
1.4	W Stöhr	29-May-2020	Reviewed by M Sharland; clarifications to 4.10. Approved.
1.5	W Stöhr	01-Dec-2020	Addition of a per-protocol analysis of the primary endpoint in response to Lancet reviewer
2.0	D Dunn, W Stöhr	02-Dec-2020	Revised version approved by M Sharland

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1 OVERVIEW OF CAP-IT

1.1 SUMMARY

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	CAP-IT
Long Title of Trial	Efficacy, safety and impact on antimicrobial resistance of duration and dose of amoxicillin treatment for young children with Community Acquired Pneumonia (CAP): a randomised controlled Trial (CAP-IT)
Study Design	Multi-centre, UK-based, randomised double-blind placebo-controlled 2x2 factorial non-inferiority trial of amoxicillin dose and duration in paediatric CAP.
Type of Participants to be Studied	Children aged greater than 6 months, weighing 6 - 24 kg with a clinical diagnosis of CAP in whom the decision has been made to treat with antibiotics. Children may have received up to 48 hours of beta-lactam antibiotics prior to randomisation, including any outpatient treatment.
Setting	Children will be recruited into two groups: 1. PED Group: children who are recruited in the Paediatric Emergency Department or Paediatric Assessment Unit (PAU). Children in this group will not receive in-hospital treatment. The CAP-IT study drug will be started on discharge from PED. 2. WARD Group: children who are recruited from inpatient paediatric hospital wards or from PAU. Children in this group will receive in-hospital treatment (oral or IV beta-lactam therapy) on the ward, or in PAU, prior to randomisation. The CAP-IT study drug will be started on discharge home from the ward or PAU.
Interventions to be Compared	Participants will be randomised at discharge from hospital to: **Randomisation 1:** • Lower dose (target dose 40mg/kg per day; range 35-50 mg/kg per day) oral amoxicillin treatment • Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment. Dose volumes will be identical in the lower and higher dose groups. **Randomisation 2:** • Three days of oral amoxicillin followed by placebo for 4 days (3 days active treatment) or • Three days of oral amoxicillin followed by a further 4 days of amoxicillin (7 days active treatment). This will result in 4 treatment groups: • Shorter + lower dose: 3 days at 35-50mg/kg/day • Longer + lower dose: 7 days at 35-50mg/kg/day • Shorter + higher dose: 3 days at 70-90mg/kg/day • Longer + higher dose: 7 days at 70-90mg/kg/day

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Study Hypothesis	1) Lower dose (35-50mg/kg/day) oral amoxicillin treatment is non-inferior to higher dose (70-90mg/kg/day) amoxicillin treatment for uncomplicated childhood CAP as determined by additional/ subsequent antibiotic treatment. 2) Shorter duration (3 days) amoxicillin treatment is non-inferior to longer duration (7 days) amoxicillin treatment for uncomplicated childhood CAP as determined by additional/ subsequent antibiotic treatment
Primary Outcome Measure(s)	Any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication up to and at final follow-up 4 weeks after randomisation.
Secondary Outcome Measure(s)	Specified clinical adverse events (including thrush, skin rashes and diarrhoea), severity and duration of parent-reported CAP symptoms; phenotypic resistance to penicillin; adherence to trial medication.
Randomisation	Children will be allocated 1:1 to each of the two factorial randomisations, separately for the PED and WARD group.
Number of Participants to be Studied	800 recruited in total. This is regarded as a minimum sample size and the TSC may decide to recruit above this number to increase statistical power and precision, resources permitting.
Duration	Children will be recruited over a period of 2-3 years and will be followed up for 28 days.
Ancillary Studies/Substudies	• Impact on gastrointestinal microflora • Diary methodology • Health economic analyses

1.2 OUTCOME MEASURES

1.2.1 PRIMARY OUTCOME MEASURE

The primary outcome is defined as any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication up to and at week 4 final follow-up (day 29).

An Endpoint Review Committee (ERC), blinded to randomised allocations, will review all cases where the participant was prescribed non-trial systemic antibacterial treatment. The main role of the Committee is to adjudicate, based on all available data, whether the primary outcome was met. Clinical indication of non-trial systemic antibacterial treatment for respiratory tract infection will be classified as "definitely/probably", or "possibly" or "unlikely" or "too little information". Those categorised as "CAP" or "other respiratory tract infection" and the likelihood that non-trial medication was indicated is "definitely/probably" or "possibly" will be regarded as fulfilling the primary endpoint.

The prescription of non-trial medication when the primary reason is (a) illness other than respiratory tract infection, (b) intolerance of or adverse reaction to trial medication, (c) parental preference, or (d) administrative error will not constitute a primary endpoint.

1.2.2 SECONDARY OUTCOME MEASURES

- Morbidity:
  - Specified clinical adverse events, including thrush, skin rashes and diarrhoea.
  - Severity and duration of parent/guardian-reported CAP symptoms.
- Microbiological:
  - Phenotypic resistance to penicillin at week 4 measured in *S. pneumoniae* isolates colonising the nasopharynx.
- Adherence to trial medication

1.3 SAMPLE SIZE

WARD and PED groups will be analysed jointly. The sample size is based on demonstrating non-inferiority for the primary efficacy endpoint for each of the duration and dose randomisations. Although inflation factors have been advocated for factorial trials to account for interaction between the interventions or a reduction in the number of events, this is not necessary if either randomised intervention (dose or duration) has a null effect (the underlying hypothesis with a non-inferiority design), as marginal analyses can then be conducted.

The underlying antibiotic re-treatment rate was originally assumed to be 5%. However, emerging data from the trial after the pilot phase suggest that the rate of the revised primary outcome is approximately 15%, without any clear difference between WARD and PED groups. Assuming a 15% event rate, 8% non-inferiority margin (on a risk difference scale) assessed against an upper 1-sided 95% CI[1], and 15% loss to follow-up, 800 children need to be randomised to achieve 90% power. This is regarded as a minimum sample size and the TSC may decide to recruit above this number to increase statistical power and precision, resources permitting.

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[1] This is equivalent to the upper 95% confidence limit (CL) or the upper bound of the two-sided 90% confidence interval (CI) ; these terms are used interchangably

2 DATA DEFINITIONS AND DERIVATIONS

2.1 DEFINITION OF BASELINE

Baseline is defined in this trial as the time of randomisation. Baseline values used to define changes over time for each participant are defined as the measurements at randomisation. If a measurement at randomisation is not available, then the measurement at pre-trial entry (WARD group) will be used.
Data collected in the period between pre-trial entry and randomisation will be reported for WARD participants as baseline data.

2.2 DEFINITION OF LAST CONTACT

For a particular participant, the last day of follow-up is defined as their latest contact with the site – in person or by telephone – or, if later, the last day of data entry on the electronic diary.

2.3 DEFINITION OF LOST TO FOLLOW-UP

A participant will be classified as lost for follow-up if it cannot be ascertained either that the participant (a) definitely DID experience the primary endpoint, or (b) definitely did NOT experience the primary endpoint i.e. if ALL of the following apply:

- no primary endpoint was confirmed at or before their last contact,
- no contact could be made in person or by telephone at the scheduled final visit
- no information about the primary endpoint could be retrieved from the participant's GP,

Participants who died or were withdrawn before day 29 will be reported separately and will not be considered as lost to follow-up.

2.4 CAP SYMPTOMS

The following CAP symptoms are elicited at pre-trial entry (WARD only), enrolment, calls at day 4, 8, 15, 22, and at the final visit, as well as at unscheduled visits: cough, wet cough (phlegm), breathing faster (shortness of breath), wheeze, sleep disturbed by cough, vomiting (including after cough), eating/drinking less, interference with normal activity. Parents/carer are asked to grade each symptom using the following five categories: not present, slight/little, moderate, bad, severe/very bad. Date of start and resolution are also asked. Symptoms and their severity (using same categories) are also asked daily on the symptom diary over a period of 14 days from randomisation.

If there is disagreement between the diary and information given during a call/visit for either (a) the date of symptom resolution, or (b) symptom severity at a given time-point, then precedence will be given to the information given during the call/visit. If symptom severity is missing in the diary, severity one day before (first choice) or one day after (second choice) will be used.

2.5 ABNORMAL VITAL PARAMETERS

Abnormal vital parameters will be defined as follows, based on standard definitions:

- Temperature: ≥38°C
- Oxygen saturation: <92%
- Heart rate: >140/min for age 1-2 years; >120/min for age ≥3 years
- Respiratory rate: >37/min for age 1-2 years; >28/min for age ≥3 years

2.6 ADVERSE EVENTS

Information about the following solicited adverse events are collected and graded in the same way as CAP symptoms (section 2.4): diarrhoea, skin rash, and thrush. In addition, adverse events related to the stop of trial medication or the start of non-trial antibiotics are recorded.

Serious adverse events (SAEs) are defined according to principles of GCP and reported on a SAE form. All SAEs reported during the trial are reviewed by the Trial Physician (blinded). SAEs are classified by system organ class and lower level term according to MedDRA® version 21.1. SAEs are graded using the Division of Aids Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table)[1], see Appendix II of CAP-IT protocol. SAEs will be analysed as episodes, with all components of the same clinical SAE presented as one episode.

2.7 PRIMARY ENDPOINT

Information about new antibacterial treatment will be collected at every call or visit, and will be reported on the Telephone Follow-up form, Unscheduled Visit form, Early Cessation form, or Final Visit form. In addition, the parents/carers are asked about any new antibacterial treatment on every day of the symptom diary.

In participants who are lost for follow-up or who have been withdrawn but given consent to use further routine data, the participant's GP will be contacted to inquire whether or not antibacterial re-treatment has been prescribed after the participant's last contact with research staff but within 4 weeks from randomisation (in line with trial follow-up). Of note, this procedure is only possible for participants enrolled on or after 1. Nov 2017, when an appropriate consent was included in the patient information sheet.

Data from all sources and prescriptions up to and including day 31 (upper limit of the visit window for the final visit; see protocol) will be considered by the ERC to define the primary endpoint (see 1.2.1).

2.8 MISSING DATA

Analyses will generally be based on observed data only. However, for the primary endpoint and for secondary outcome data which are missing in >10% participants, reasons for any missing data will be described, the relevant predictors explored, and imputation methods considered (see Analysis Details).

3 ANALYSIS PRINCIPLES

This analysis plan is based on version 4.0 of the CAP-IT protocol, which stipulates a joint analysis of the PED and WARD strata.

- The primary analyses will be modified intention-to-treat (mITT), i.e. including all patients enrolled and analysed according to the group to which they were randomised regardless of treatment actually received. The one modification to the strict ITT principle is the exclusion of randomised patients who did not take any trial medication. Since this is a blinded trial, the risk of introducing bias by exclusion of these patients is minimal, however, the number of such cases and their details will be described. As non-adherence to allocated treatment can dilute treatment effects, which is of particular concern in non-inferiority trials, an on-treatment analysis will be also performed. For some secondary endpoints, including adverse events and resistance, on-treatment analyses will be performed as well as ITT analyses.
- Outcomes, for primary and secondary endpoints, will be presented according to the four randomised groups. "Main effects" for the two randomisations will be estimated by collapsing across levels of the other randomisation group. This will be supplemented by tests for interaction between the two randomisations and with previous systemic antibacterial exposure. The latter variable will be examined both as a binary factor (yes/no) and as an ordered categorical variable (time since first antibacterial prescription to randomisation). The estimated main effects will be re-interpreted if any of the tests for interaction show a trend towards statistical significance (e.g. $p<0.1$).
- Formal statistical adjustment for multiple comparisons (particularly pertinent for some of the secondary endpoints) will not be applied, although significance tests will be interpreted in the context of the total number of related comparisons performed.
- For continuous variables, the following will be presented by scheduled calls/visits and by randomised group: mean (SD) or median (IQR) of absolute values and of changes in absolute values from baseline.
- Binary and categorical variables will be tabulated by randomised group. Differences between groups at particular time-points will be tested using chi-squared tests (or exact tests if appropriate). For binary variables, logistic regression models will be used for adjusted analyses. Generalised Estimating Equations will be used for a global test of difference between treatment groups across all calls/visits, excluding baseline values.
- Ordered variables will be tabulated, overall and by randomised group. Differences between groups at particular time-points will be tested using rank tests, and ordered logistic regression models for adjusted analyses. Random-effects ordered logistic models will be used for a global test of difference between treatment groups across all calls/visits.
- Time-to-event outcomes will consider time from baseline to the event date, using Kaplan-Meier estimation. For participants who do not experience the event in question, data will be censored at the date of last review of the particular event. Differences between groups will be tested using a log-rank test and Cox proportional hazard regression models. For outcomes of specific interest, the difference in median survival time between groups will also be estimated.
- The analysis and interpretation of the analyses will emphasise confidence intervals rather than significance testing. For the primary endpoint, assessment of non-inferiority will be supplemented by significance tests (under the null hypothesis of no difference) whether or not non-inferiority is demonstrated.[2,3] For secondary endpoints, all significance tests will be performed under the standard null hypothesis of no difference (i.e. effectively superiority comparisons).

- The analyses described in this document focus on the pre-specified primary and secondary outcomes. Additional analyses may be conducted to shed further light on the interpretation of the trial results, including mechanistic processes. These analyses are not possible to pre-specify since they depend on what is actually observed.
- All estimates, including differences between randomised groups, will be presented with 2-sided 90% confidence intervals (rather than the more conventional 95%).[4] This is to achieve consistency with the reporting of the primary endpoint (section 4.6).
- All statistical tests will be 2-sided. P values will be given to 2 decimal places if ≥0.10, otherwise to 1 significant figure

4 ANALYSIS DETAILS

The following results will be presented overall, and by randomisation arm.

4.1 ENROLMENT AND ELIGIBILITY

- Total enrolled by site, with dates of first and latest enrolment
- Enrolment over calendar time: cumulative enrolment; enrolment by calendar month
- Eligibility: number (%) and reasons for any ineligibilities (i.e. enrolled although eligibility criteria violated)

4.2 PATIENT CHARACTERISTICS

The following baseline characteristics will be presented overall and by randomised group. In general, for the grouping of quantitative variables, categories will be chosen after univariate inspection of the data, ensuring that a reasonable number of participants are represented in each category. An exception to this rule are the variables with clinically accepted cut-offs, as described in Section 2.

- Stratum: number (%) PED, WARD
- Age: median (IQR), range; distribution in categories
- Sex: number (%) male, female
- Weight: median (IQR), range; distribution in categories
- Ethnicity: number (%) White, Asian or British Asian, Black or Black British, mixed ethnic group, other
- Treatment with systemic antibacterials in the last 3 months: number (%) treated
- Treatment with systemic antibacterials in last 48 hours: number (%) treated; time since first dose, duration of treatment: median (IQR), range; number of doses received: number (%)
- Other treatments during admission prior to enrolment (supportive measures, non-antibacterial treatment): number (%) treated; duration of treatment.
- Medical history: number (%) with underlying disease; number (%) with routine vaccination; duration of cough and temperature: median (IQR)
- Vital Parameters, median (IQR), range: temperature; heart rate; respiratory rate; oxygen saturation
- Physical examinations, number (%) with: nasal flaring; chest retractions; pallor; stridor; inflamed/bulging tympanic membrane or middle ear effusion; coryza; enlarged tonsils or pharyngitis. These will also be combined into signs of upper respiratory tract infection (stridor, inflamed/bulging tympanic membrane, coryza, pharyngitis) and signs of respiratory distress (nasal flaring, chest retractions, grunting).
- Chest examination, number (%) in categories absent, unilateral, bilateral, not assessed: dullness to percussion; bronchial breathing; reduced breath sounds; crackles/crepitations

4.3 DESCRIPTION OF FOLLOW-UP

- Time between randomisation and last day of follow-up (days): median (IQR), range
- Attendance of scheduled calls, by day in trial (day 4, 8, 15, 22): number (%) missed calls/visits.
- Final visit: number (%) happened/missed; number (%) attended in clinic/assessed by telephone/happened at the participant's home
- Denominator to include any patients withdrawn or lost to follow-up, but not any known to have died.

- Additional visits compared with schedule: number (%). Denominator to include visits for any patients withdrawn or lost to follow-up, but not any known to have died.
- Withdrawal from trial participation: number (%); description of reasons.

4.4 DESCRIPTION OF DEVIATIONS TO RANDOMISED TRIAL TREATMENT

- Not started trial medication as randomised: number (%).
- Early and permanent discontinuation of trial medication: number (%). Reason for discontinuation: number (%).
- Dose deviations, overall and by bottle (bottle A (Day 1-3); bottles B/C (Day 4-7)): number (%) of participants who ever missed a dose; number of missed doses per participant; missed doses as proportion of scheduled doses per participant.
- Volume deviations, overall and by bottle (bottle A; bottles B/C): number (%) of participants who ever reported a deviation from prescribed volume; number (%) of participants who ever reported giving smaller than the prescribed volume; number (%) of participants who ever reported giving more than the prescribed volume; description of doses affected.
- Overall non-adherence to trial medication, for the purposes of the on-treatment analysis of the primary endpoint, is defined as having taken less than 80% of trial medication as scheduled (i.e. more than 2 doses not taken or taken at smaller volume). However, switch from trial medication to non-trial antibiotics due to deterioration will not be regarded as non-adherence.
- Non-adherence will be analysed in two ways: 1) based on all trial medication including placebo, and 2) based on active drug only.

4.5 DESCRIPTION OF NON-TRIAL ANTIBACTERIAL TREATMENT

- Systemic antibacterial treatment other than trial medication: number (%).
- Type of antibacterial (if recorded)
- Prescriber of non-trial antibacterial treatment: CAP-IT investigator, other hospital doctor, GP.
- Reason for starting non-trial antibacterial treatment (as adjudicated by the ERC): number (%) in categories: a) CAP, b) other respiratory tract infection (not CAP), c) other bacterial infection, d) other illness/injury, e) intolerance to IMP/adverse event, f) parental preference, g) admin/pharmacy error
- Likelihood that the reported non-trial systemic antibacterial was clinically indicated (for reasons a) & b), as adjudicated by the ERC)
- Cumulative number of additional courses of systemic antibacterials

4.6 PRIMARY ENDPOINT

The primary outcome is defined as any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication up to and including week 4 final follow-up (Section 1.2).

4.6.1 NON-INFERIORITY

The trial was designed to test the following hypotheses in terms of the primary endpoint:

1) Lower dose oral amoxicillin treatment (35-50mg/kg/day) is non-inferior to higher dose treatment (70-90 mg/kg/day).
2) Shorter duration (3 days) amoxicillin treatment is non-inferior to longer duration (7 days) treatment.

Lower dose treatment and shorter duration will be will be considered "non-inferior" to higher dose and longer duration treatment, respectively, if the upper 95% confidence limit (of the 2-sided 90% confidence interval) for the difference in the proportion of children with the primary endpoint at day 29 is less than the non-inferiority margin of 8%.

Although the non-inferiority margin is critical to the design of the trial, it is less relevant to its interpretation. This will instead be largely based on the observed confidence interval for the difference in proportions.[5]

4.6.2 ANALYSIS

Randomised groups will be compared using time to event methods, analysing time from enrolment to the first occurrence of the primary endpoint. Participants with incomplete primary outcome data (i.e. missed the final visit; did not have the primary outcome reported by the time of their last contact; and whose GPs could not be contacted or did not respond when contacted about antibacterial treatment within 4 weeks from baseline) will be censored at the time of their last contact. For participants who missed the final visit in the trial but who have confirmation from their GP that no additional antibacterials have been prescribed within 4 weeks from baseline, day 29 will be the censoring date.

The proportion of children with the primary endpoint, the risk difference between groups at day 29, will be derived from Kaplan-Meier estimates. Standard errors (and confidence intervals) for the risk difference will be derived from the estimated standard errors of the individual survival functions, based of the log(-log) transformation, as implemented in STATA (**stsurvdiff** command).[6]

Potential interaction effects with the other randomisation and previous antibacterial exposure will be examined (see 3. Analysis Principles).

4.6.3 ADDITIONAL HANDLING OF INCOMPLETE DATA

Standard time to event methods assume independent censoring. In secondary analyses, multiple imputation methods will be explored to estimate the primary outcome status at day 29. Such methods are useful only if powerful predictors of primary outcome status are identified, and results will be presented only if this is found to be the case. Potential predictors to be examined will include prior antibacterial treatment, and severity of symptoms at previous calls/visits.

4.6.4 ON-TREATMENT ANALYSES FOR THE PRIMARY ENDPOINT

The on-treatment analysis will exclude participants who were non-adherent to trial medication as defined in 4.4.

4.6.5 SENSITIVITY ANALYSES FOR THE PRIMARY ENDPOINT

The primary analysis of the primary endpoint will include only those endpoints accepted by the ERC. The following sensitivity analyses for the primary endpoint will be performed:

1) Including all systemic antibacterial treatments other than trial medication regardless of reason and indication.
2) Including only ERC-adjudicated clinically indicated systemic antibacterial treatment where either CAP or "chest infection" is specified as a reason for this treatment (rather than any respiratory tract infection).

3) As 2) but including as an endpoint all systemic antibacterial treatments for CAP or "chest infection" where the clinical indication was 'unlikely' as adjudicated by the ERC.
4) Starting non-trial antibacterial treatment within the first 3 days from randomisation for any reason cannot by definition be related to the treatment duration randomisation. Sensitivity analyses will be performed ignoring these early endpoints for the comparison of shorter versus longer treatment.

4.6.6 SUBGROUP ANALYSES FOR THE PRIMARY ENDPOINT

1) A subgroup analysis will consider the severity of CAP at enrolment and the main efficacy analysis repeated, limited to participants at the higher end of the severity spectrum. This is to provide reassurance that an overall null effect (if observed) is not due to a dilution effect arising from the inclusion of children with mild disease, possibly related to viral aetiology. However, there is no widely accepted classification for defining the severity of paediatric CAP in high income settings. Thus the definition of severe/less severe subgroups will be based on the total number of the following signs/symptoms that are abnormal: respiratory rate, oxygen saturation, chest retractions. Further work, not planned for inclusion in the primary publication, will consider more sophisticated statistical approaches (e.g. principal component analysis , latent class analysis) that may also consider post-randomisation data.

2) Related to (1), since there are potentially different infections across the winter, efficacy analyses will additionally be stratified by calendar time. This stratification will be based on PHE reports of circulating viruses/bacteria in the winter seasons spanned by CAP-IT.

4.7 SECONDARY ENDPOINTS: CAP SYMPTOMS

The following analyses will be performed for each symptom:

- Severity of a symptom: number (%) in severity categories at every scheduled contact (day 4 and day 8 of particular interest). Analysed as for ordinal outcomes as specified in section 3.
- Duration of a symptom: Time from baseline to resolution. Resolution is defined as the first day the symptom is reported not present. Analysed as time to event outcome as specified in section 3. If a symptom is not present at enrolment, participants will be excluded from the respective analysis. Symptom resolution within the first 3 days from randomisation cannot by definition be related to the treatment duration randomisation. Sensitivity analyses will be performed changing the time origin to day 4 for the comparison of shorter versus longer treatment.

4.8 SECONDARY ENDPOINTS: CLINICAL ADVERSE EVENTS

Adverse events post-randomisation will be presented overall and by randomised arm. For all adverse event types, the total number of events, the number of participants with at least one event, the number of participants with at least one new event, and the maximum grade per participant will be given. Analysis of adverse event outcomes will be based on the number ever experienced a type of adverse event which will be compared as for binary outcomes. Timing of events, and recurrent events will also be described.

Where relevant and established, events will also be presented by severity grade, and by relationship to study treatment (definitely, probable, possible, unlikely, unrelated).

The following adverse event outcomes will be analysed:

- Diarrhoea
- Skin rash
- Thrush
- Treatment-modifying adverse events

A line listing will be produced of abnormalities detected on clinical investigations e.g. chest x-ray, haematology, biochemistry, blood culture. These are not mandated by the protocol and are likely be infrequently reported during follow-up.

4.9 SECONDARY ENDPOINTS: SERIOUS ADVERSE EVENTS

- Number of participants with at least one SAE: compared as for binary outcomes.
- Description of the type of SAE (fatal, life-threatening, hospitalisation, disability, other).
- Description of severity grade, and relationship to study treatment (definitely, probable, possible, unlikely, unrelated).

4.10 SECONDARY ENDPOINTS: *S. PNEUMONIAE* CARRIAGE AND ANTIMICROBIAL RESISTANCE

S. pneumoniae carriage and resistance to penicillin will be assessed from nasopharyngeal samples. All nasopharyngeal samples are screened for *S. pneumoniae* carriage at the University of Bristol, and the species confirmed at the University of Antwerp. *S. pneumoniae* carriage will be assumed only if identified in both laboratories. Resistance is measured with a broth microdilution technique (0.016-16 mg/L) in terms of minimal inhibitory concentrations (MIC). This is categorised using cut-offs proposed by European Committee on Antimicrobial Susceptibility Testing for pencillin and amoxicillin resistance to S. Pneumoniae [7]:

1) Penicillin: Sensitive (S): MIC ≤ 0.064; Intermediate (I): MIC 0.125 to 2; Resistant (R): MIC > 2
2) Amoxicillin: S: MIC ≤ 0.5; I: MIC = 1; R: MIC > 1

4.10.1 DATA COMPLETENESS

Overall, and for each randomisation group, the number (%) of participants with a sample taken and tested (cultured) will be calculated for (a) baseline, (b) the final visit, and (c) combination of baseline and final visit.

4.10.2 BASELINE

Baseline samples on some participants (predominantly WARD) will have been collected after up to 48 hours exposure to antibacterials. Exploratory analyses will first be performed to examine if carriage rates and/or resistance is affected by prior exposure (and duration of exposure). Further analyses will be stratified by prior antibacterial exposure if differences are found.

The following descriptive analyses will be presented overall and by randomisation group.

- Number (%) of samples with positive *S. pneumoniae* culture

- Frequency distribution of MIC values for both penicillin and amoxicillin: median (IQR, range); mean (sd) of log-transformed MIC
- Number (%) of samples classified as S/I/R using the cut-offs described above (denominator: samples with positive S. pneumonia culture), for both penicillin and amoxicillin.

4.10.3 FINAL VISIT

Two sets of analyses will be performed: (1) including all participants, and (2) excluding participants who received additional non-IMP antibacterials (findings on this group will also be presented as a line listing). Analysis (1) will be considered as the primary analysis. All analyses will be presented by randomisation group.

***S. pneumoniae* carriage**

- Tabulation of the number (%) of samples with positive *S. pneumoniae* culture at the final visit. Groups will be compared using tests for binary variables, as described in Section 3.
- Cross-tabulation of *S. pneumoniae* culture results at the final visit versus *S. pneumoniae* culture results at baseline (including missing values). It is envisaged that this will be a descriptive analysis only, without statistical modelling or significance testing.

Antimicrobial resistance

The following descriptive analyses will be presented overall and by randomisation group for both penicillin and amoxicillin resistance:

- Frequency distribution of MIC values: median (IQR, range); mean (sd) of log-transformed MIC
- Number (%) of samples with resistance (S versus combined I or R) at the final visit. This analysis will be performed using two different denominators:
    - limited to participants with a positive *S. pneumoniae* culture result
    - all participants with a sample, including those negative for *S. pneumoniae*

  Groups will be compared by tests for binary variables.

- Cross-tabulation of resistance (S, I/R, or missing) at the final visit versus resistance (S, I/R, or missing) at baseline. This will be a descriptive analysis only (i.e. without statistical modelling).
- Change in log(MIC) in participants in whom this parameter is measured at both the baseline and the final visit. This will be analysed with randomisation group as factors and adjusting for the baseline result. Since not all patients will contribute to this analysis it will require careful interpretation, especially if carriage rates differ between randomisation groups.

4.11 ANCILLARY STUDIES/SUBSTUDIES

The analysis of the following ancillary studies / substudies will be described in a separate analysis plans:

- Impact on gastrointestinal microflora
- Diary Methodology
- Health-economics

5 REFERENCES

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