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Effect of Amoxicillin Dose and Treatment Duration on the Need for Antibiotic Re-treatment in Children With Community-Acquired Pneumonia
The CAP-IT Randomized Clinical Trial

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IMPORTANCE The optimal dose and duration of oral amoxicillin for children with community-acquired pneumonia (CAP) are unclear.

OBJECTIVE To determine whether lower-dose amoxicillin is noninferior to higher dose and whether 3-day treatment is noninferior to 7 days.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, 2 × 2 factorial noninferiority trial enrolling 824 children, aged 6 months and older, with clinically diagnosed CAP, treated with amoxicillin on discharge from emergency departments and inpatient wards of 28 hospitals in the UK and 1 in Ireland between February 2017 and April 2019, with last trial visit on May 21, 2019.

INTERVENTIONS Children were randomized 1:1 to receive oral amoxicillin at a lower dose (35-50 mg/kg/d; n = 410) or higher dose (70-90 mg/kg/d; n = 404), for a shorter duration (3 days; n = 413) or a longer duration (7 days; n = 401).

MAIN OUTCOMES AND MEASURES The primary outcome was clinically indicated antibiotic re-treatment for respiratory infection within 28 days after randomization. The noninferiority margin was 8%. Secondary outcomes included severity/duration of 9 parent-reported CAP symptoms, 3 antibiotic-related adverse events, and phenotypic resistance in colonizing *Streptococcus pneumoniae* isolates.

RESULTS Of 824 participants randomized into 1 of the 4 groups, 814 received at least 1 dose of trial medication (median [IQR] age, 2.5 years [1.6-2.7]; 421 [52%] males and 393 [48%] females), and the primary outcome was available for 789 (97%). For lower vs higher dose, the primary outcome occurred in 12.6% with lower dose vs 12.4% with higher dose (difference, 0.2% [1-sided 95% CI −∞ to 4.0%]), and in 12.5% with 3-day treatment vs 12.5% with 7-day treatment (difference, 0.1% [1-sided 95% CI −∞ to 3.9]). Both groups demonstrated noninferiority with no significant interaction between dose and duration (P = .63). Of the 14 prespecified secondary end points, the only significant differences were 3-day vs 7-day treatment for cough duration (median 12 days vs 10 days; hazard ratio [HR], 1.2 [95% CI, 1.0 to 1.4]; P = .04) and sleep disturbed by cough (median, 4 days vs 4 days; HR, 1.2 [95% CI, 1.0 to 1.4]; P = .03). Among the subgroup of children with severe CAP, the primary end point occurred in 17.3% of lower-dose recipients vs 13.5% of higher-dose recipients (difference, 3.8% [1-sided 95% CI, −∞ to10%]; P value for interaction = .18) and in 16.0% with 3-day treatment vs 14.8% with 7-day treatment (difference, 1.2% [1-sided 95% CI, −∞ to 7.4%]; P value for interaction = .73).

CONCLUSIONS AND RELEVANCE Among children with CAP discharged from an emergency department or hospital ward (within 48 hours), lower-dose outpatient oral amoxicillin was noninferior to higher dose, and 3-day duration was noninferior to 7 days, with regard to need for antibiotic re-treatment. However, disease severity, treatment setting, prior antibiotics received, and acceptability of the noninferiority margin require consideration when interpreting the findings.

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Visual Abstract

Supplemental content

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Children younger than 5 years commonly receive oral antibiotics, mainly for respiratory infections.[1,2] In a retrospective cohort study from the UK, the Netherlands, and Belgium, and repeated point-prevalence surveys conducted in 28 European emergency departments (EDs) between 2014 and 2016, 10% to 40% of children with infection symptoms were diagnosed with possible serious bacterial infections requiring antibiotics, compared with less than 5% in primary care, and the lower respiratory tract was the second most common focus.[3,4]

Bacteria have been causally implicated in approximately one-third of community-acquired pneumonia (CAP) cases among children younger than 5 years admitted to the hospital, with codetection of viruses and bacteria being common in symptomatic and asymptomatic young children.[5-7] Neither chest radiographs nor inflammatory biomarkers differentiate which children with CAP require antibiotics.[8-10] The lack of predictive diagnostic tests to rule out or confirm the need for antibiotics means that young children with clinical signs of CAP are likely to continue to be prescribed antibiotics, especially in hospitals. Optimizing antibiotic treatment to minimize drug exposure while achieving high rates of clinical cure would inform essential antibiotic stewardship interventions.

Amoxicillin is widely recommended as the first-line antibiotic for CAP in young children.[11-13] Randomized clinical trial evidence from low- and middle-income countries supports treatment duration of 3 to 5 days in mild or moderate disease.[14,15] However, the most appropriate total daily dose of oral amoxicillin treatment has not been investigated in any trial, and it is unclear whether evidence supporting 3-day treatment can be generalized from low- and middle-income countries to high-income secondary care settings with differing diagnostic criteria.[11-13] The CAP-IT trial (Community-Acquired Pneumonia: a randomized controlled trial) aimed to evaluate whether lower dose and shorter amoxicillin treatment were noninferior to higher dose and longer treatment, with regard to the need for antibiotic re-treatment within 28 days.

Key Points

Question For children with community-acquired pneumonia discharged from an emergency department, observational unit, or inpatient ward (within 48 hours), is subsequent outpatient treatment with oral amoxicillin at a dose of 35 to 50 mg/kg per day noninferior to 70 to 90 mg/kg per day, and is a 3-day course noninferior to 7 days, with regard to the need for antibiotic re-treatment?

Findings In this 2 × 2 factorial randomized clinical trial of 814 children requiring amoxicillin for community-acquired pneumonia at hospital discharge, antibiotic re-treatment within 28 days occurred in 12.6% vs 12.4% of those randomized to lower vs higher doses, and in 12.5% vs 12.5% of those randomized to 3-day vs 7-day amoxicillin duration. Both comparisons met the prespecified 8% noninferiority margin.

Meaning Among children with community-acquired pneumonia discharged from an emergency department, observational unit, or inpatient ward, further outpatient treatment with oral amoxicillin at a dose of 35 to 50 mg/kg per day was noninferior to a dose of 70 to 90 mg/kg per day and 3 days was noninferior to 7 days with regard to the need for later antibiotic re-treatment.

Methods

Study Design

This was a multicenter, randomized, blinded, placebo-controlled, 2 × 2 factorial, noninferiority trial conducted in 28 hospitals in the UK and 1 in Ireland, comparing total daily amoxicillin dose (35-50 mg/kg or 70-90 mg/kg) and duration (3 or 7 days) for treatment of childhood CAP. The trial protocol was approved by the West London and GTAC (Gene Therapy Advisory Committee) research ethics committee (16/LO/0831) (Supplement 1).[16] Parents or legal guardians of participating children provided written informed consent prior to any study procedures.

Participants

Children were eligible if they were older than 6 months of age, weighed 6 to 24 kg, were clinically diagnosed with CAP, and treatment with amoxicillin monotherapy on discharge from hospital ED, observational unit, or inpatient ward was planned. Consistent with British Thoracic Society guidelines, CAP was defined as (1) parent- or guardian-reported cough within the previous 96 hours; (2) measured temperature of 38 °C or parent- or guardian-reported fever within previous 48 hours; and (3) signs of labored or difficult breathing or focal chest sign(s) (eTable 1 in Supplement 2).[12] Enrollment took place at discharge if inclusion and exclusion criteria were met (eMethods 2 in Supplement 2). Exclusion criteria were (1) uninterrupted prior β-lactam antibiotic treatment for more than 48 hours or any prior non-β-lactam treatment; (2) severe underlying chronic disease; (3) any contraindications to amoxicillin, including allergy; (4) complicated pneumonia (defined as signs of sepsis or local parenchymal or pleural complications); or (5) bilateral wheezing without focal chest signs.

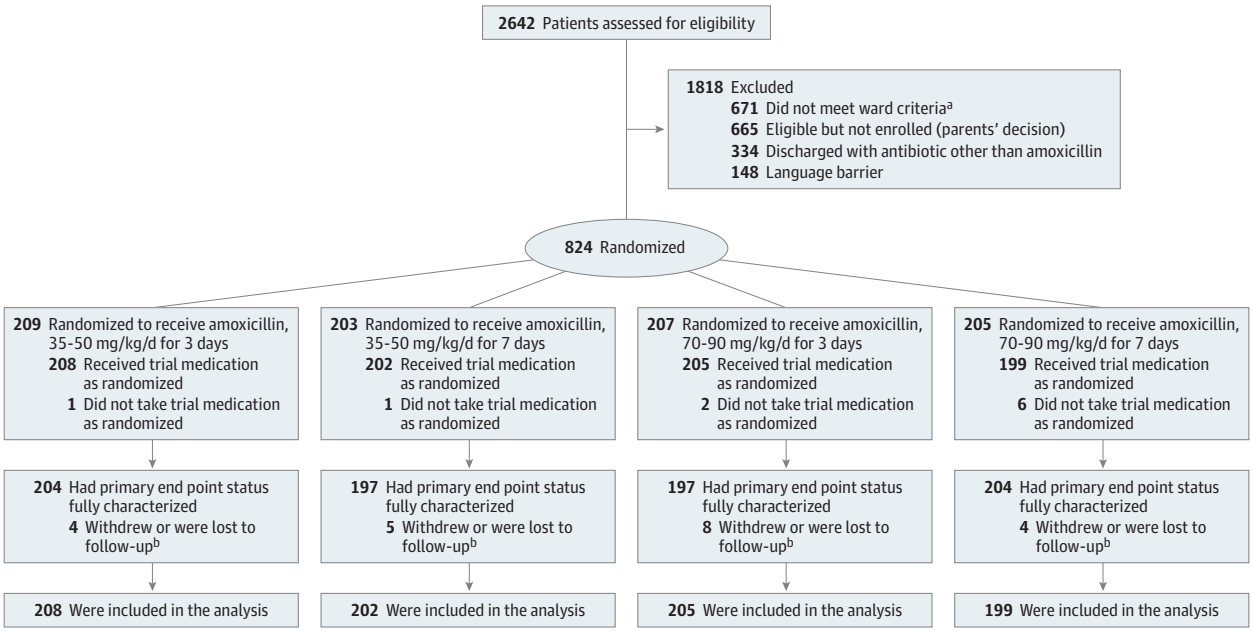
Information on race and ethnicity was collected based on UK Census options through participant self-identification. The reason for collecting this information is because outcomes for acute infections and respiratory disease in the UK and US have been reported to be poorer among children from racial and ethnic backgrounds other than White.[17,18]

Randomization and Blinding

A computer-generated randomization list was produced by the trial statistician based on blocks of 8 and containing an equal number of the 4 possible combinations of dose and duration in random order. Participants were randomized simultaneously to each of the 2 factorial randomizations in a 1:1 ratio by dispensing the next sequentially numbered set of trial drug bottles. Randomization was stratified by study site and whether or not patients had received any nontrial antibiotics in the hospital before being enrolled.

Blinding was achieved by independent rebottling, packaging, and labeling of 2 amoxicillin brands, and trial kits were assigned sequential numbers based on the randomization list and delivered ready to dispense to site pharmacies. Lower and higher drug doses were achieved by administering the same volume according to a weight-banded dosing chart (eTable 2

Figure 1. Patient Recruitment, Randomization, and Follow-up in the CAP-IT Trial



[a] Ward criteria indicates children recruited from inhospital pediatric wards or units with an inpatient stay longer than 48 hours and treated with non–β-lactam antibiotics as inpatients.

[b] Follow-up included time up to withdrawal.

in Supplement 2) using 125 mg/5mL and 250 mg/5mL amoxicillin suspension, which were otherwise of identical appearance, smell, and taste. In an effort to ensure blinding for the duration comparison, a single amoxicillin brand was used for the first 3 days, followed by a different amoxicillin-containing suspension (of the same concentration) or a matching placebo suspension for days 4 to 7.

Procedures

Children were screened against eligibility criteria during ED or hospital admission by trained staff assessing the parent- or guardian-reported history and physical examination. No radiological or laboratory diagnostic tests were mandated, but results were collected if done as part of routine care. A nasopharyngeal swab for *Streptococcus pneumoniae* carriage and resistance was taken at enrollment prior to administration of the study drug.

Follow-up data were collected during scheduled telephone calls 3, 7, 14, and 21 days after discharge and by face-to-face visit (or telephone call if a visit was not possible) on day 28 and in case of unplanned reattendances or readmissions. At all follow-up contacts, information was collected regarding CAP symptoms, adverse events, trial medication adherence, and any nontrial antibiotic prescriptions. Parents and guardians were provided with a diary (paper or electronic) to be completed during the first 14 days in which they recorded CAP symptom data plus information on health service utilization. At the 28-day visit, a repeat nasopharyngeal swab was collected. Primary care physicians were asked about nontrial antibiotic prescriptions if the 28-day visit was missed, provided written consent had been given.

Nasopharyngeal swabs were frozen at below −20 °C within 6 hours of being obtained. Samples were batched and sent to the Children's Vaccine Centre, Bristol University, for screening culture. All *S pneumoniae* isolates were then transferred to the University of Antwerp for confirmatory analysis and for penicillin and amoxicillin susceptibility testing, interpreted according to EUCAST Clinical Breakpoint Tables version 10.0 as sensitive, nonsusceptible, or resistant (eMethods 2 in Supplement 2).[19]

Outcomes

The primary end point was clinically indicated treatment with systemic antibiotics (other than trial medication) for a respiratory tract infection, including CAP, within 28 days of randomization. All primary end points were reviewed by an end point review committee, blinded to treatment allocation, to adjudicate whether treatment was clinically indicated and prescribed for respiratory tract infection.

The secondary end points were as follows: (1) severity (graded as not present, slight/little, moderate, bad, severe/very bad) and duration (with the first day the symptom is reported not present defined as resolved) of 9 parent-reported CAP symptoms (fever, cough, phlegm, fast breathing, wheezing, disturbed sleep, eating/drinking less, interference with normal activity, vomiting); (2) potential amoxicillin-related clinical adverse events (diarrhea, thrush, skin rash); (3) adherence to trial medication (eMethods 2 in Supplement 2); and (4) phenotypic penicillin nonsusceptibility or resistance at 28 days in nasopharyngeal *S pneumoniae* isolates (eMethods 3 in Supplement 2). The prespecified analysis also included serious adverse events.

Table 1. Participant Characteristics at Baseline or Presentation (for Inpatients)

	Amoxicillin dosing and duration[a]			
	35-50 mg/kg/d for 3 Days (n = 208)	35-50 mg/kg/d for 7 Days (n = 202)	70-90 mg/kg/d for 3 Days (n = 205)	70-90 mg/kg/d for 7 Days (n = 199)
Demographics				
Age, median (IQR), y	2.5 (1.7-3.7)	2.6 (1.6-3.9)	2.5 (1.7-3.8)	2.3 (1.4-3.6)
Male sex	110 (53)	100 (50)	107 (52)	104 (52)
Female sex	98 (47)	102 (50)	98 (48)	95 (48)
Race and ethnicity				
Asian or British Asian	32 (15)	23 (11)	21 (10)	30 (15)
Black or Black British	20 (10)	20 (10)	20 (10)	16 (8)
Multiracial	15 (7)	17 (8)	14 (7)	14 (7)
White	139 (67)	136 (67)	144 (70)	135 (68)
Other[b]	2 (1)	6 (3)	6 (3)	4 (2)
Medical history				
Asthma or inhaler use within past month	54 (26)	65 (32)	71 (35)	65 (33)
Allergy or eczema	52 (25)	63 (31)	56 (27)	58 (29)
Prematurity	26 (13)	17 (8)	25 (12)	18 (9)
Other underlying disease	16 (8)	21 (10)	5 (2)	14 (7)
Routine vaccinations				
Yes	198 (95)	190 (94)	196 (96)	189 (95)
No	8 (4)	6 (3)	7 (3)	5 (3)
Unknown	2 (1)	6 (3)	2 (1)	5 (3)
History of current concern				
Duration of cough, median (IQR), d	4 (2-7)	4 (2-6)	4 (3-7)	4 (2-7)
Duration of fever, median (IQR), d	2 (2-4)	3 (1-4)	3 (2-4)	2 (1-4)
Systemic antibiotics in last 3 mo	30 (14)	34 (17)	36 (18)	29 (15)
Systemic antibiotics in last 48 h	61 (29)	58 (29)	62 (30)	61 (31)
<12 h	34 (56)	33 (57)	34 (55)	32 (52)
12-<24 h	15 (25)	12 (21)	18 (29)	15 (25)
≥24 h	12 (19)	13 (23)	10 (16)	14 (23)
Clinical examination				
Weight, median (IQR), kg	13.9 (11.5-16.5)	13.4 (11.2-17.0)	13.8 (11.5-16.4)	13.0 (10.7-15.9)
Temperature, median (IQR), °C	38.2 (37.3-38.8)	38.0 (37.2-38.9)	37.9 (37.0-38.6)	38.1 (37.4-38.7)
Abnormal temperature[c]	121 (58)	106 (52)	100 (49)	114 (57)
Heart rate, median (IQR), beats/min	146 (133-160)	146 (130-161)	140 (129-153)	146 (131-162)
Abnormal heart rate[c]	154 (74)	153 (76)	128 (62)	143 (72)
Respiratory rate, median (IQR), breaths/min	38 (30-44)	37 (30-44)	36 (30-42)	40 (32-46)
Abnormal respiratory rate[c]	138 (66)	132 (65)	124 (61)	134 (68)
Oxygen saturation, median (IQR), %	96 (95-98)	96 (95-98)	97 (95-98)	96 (94-98)
Abnormal oxygen saturation[c]	7 (3)	11 (5)	11 (5)	14 (7)
Nasal flaring	18 (9)	15 (7)	17 (8)	25 (13)
Chest retractions	117 (57)	122 (60)	122 (60)	122 (61)
Pallor	48 (23)	34 (17)	45 (22)	42 (21)
Dullness to percussion				
Absent	105 (85)	89 (86)	93 (87)	93 (85)
Unilateral	18 (15)	14 (14)	13 (12)	14 (13)
Bilateral	0	0	1 (1)	2 (2)
Bronchial breathing				
Absent	146 (83)	137 (80)	130 (82)	133 (82)
Unilateral	23 (13)	30 (18)	26 (16)	24 (15)
Bilateral	6 (3)	4 (2)	2 (1)	5 (3)
Reduced breath sounds				
Absent	108 (54)	94 (49)	94 (48)	93 (50)
Unilateral	82 (41)	86 (45)	92 (47)	76 (41)
Bilateral	10 (5)	10 (5)	10 (5)	16 (9)

(continued)

Table 1. Participant Characteristics at Baseline or Presentation (for Inpatients) (continued)

	Amoxicillin dosing and duration[a]			
	35-50 mg/kg/d for 3 Days (n = 208)	35-50 mg/kg/d for 7 Days (n = 202)	70-90 mg/kg/d for 3 Days (n = 205)	70-90 mg/kg/d for 7 Days (n = 199)
Crackles/crepitations				
Absent	37 (18)	32 (16)	34 (17)	31 (16)
Unilateral	147 (72)	140 (70)	143 (72)	132 (68)
Bilateral	20 (10)	28 (14)	22 (11)	30 (16)

[a] Numeric values are presented as No. (%) unless othwise indicated.

[b] For race and ethnicity, other includes Middle Eastern/North African (n = 12), Latin American (n = 3), and children with missing data (n = 3).

[c] Abnormal parameters are reported for the following clinical measures: temperature (≥38 °C), 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), and oxygen saturation (<92%).

Sample Size Calculation

The trial was designed to demonstrate noninferiority of lower dose compared with higher dose, and shorter duration compared with longer duration, in terms of the primary end point. The noninferiority margin was defined as a risk difference of 8% assessed against a 1-sided 95% CI.[20] Given a 15% antibiotic re-treatment rate based on internal pilot data, 15% loss to follow-up, and assuming no interaction between the dose and duration interventions, the sample size of 800 participants was estimated to achieve 90% power.

As it was unclear at trial initiation what the primary end point rate would be, data from a preplanned internal pilot phase were reviewed by the independent data monitoring committee (eMethods 4 in Supplement 2). After 227 children were enrolled (160 from the ED, 67 after inpatient stay), it was noted that disease severity at enrollment was not significantly different among children from each clinical pathway (eMethods 5 in Supplement 2), and the re-treatment end point rate of 15% was higher than the 5% rate originally assumed. The data and safety monitoring committee, with support from the trial steering committee, recommended the following amendments: (1) joint analysis of children immediately discharged from the ED and discharged after an inpatient stay (eMethods 5 in Supplement 2); and (2) revision of the noninferiority margin from 4% to 8% to be closer to the most conservative 10% noninferiority margin recommended by the Infectious Diseases Society of America for noninferiority trials in CAP with a mortality end point (eMethods 6 in Supplement 2). For binary clinical end points, a noninferiority margin of up to 20% could be acceptable per the Infectious Diseases Society of America.[21]

Statistical Design and Analysis

The primary analysis included only participants who received the trial drug, and patients were analyzed in the groups to which they were randomized. The proportion of children meeting the primary end point was obtained from the cumulative incidence at day 28 as estimated by Kaplan-Meier methods accounting for loss to follow-up. The main effect of each randomization was estimated by collapsing across levels of the other randomization factor, after checking for the absence of statistical interaction between the 2 randomizations. Other tests for additive interaction were also prespecified for each randomization group with previous systemic antibacterial exposure.

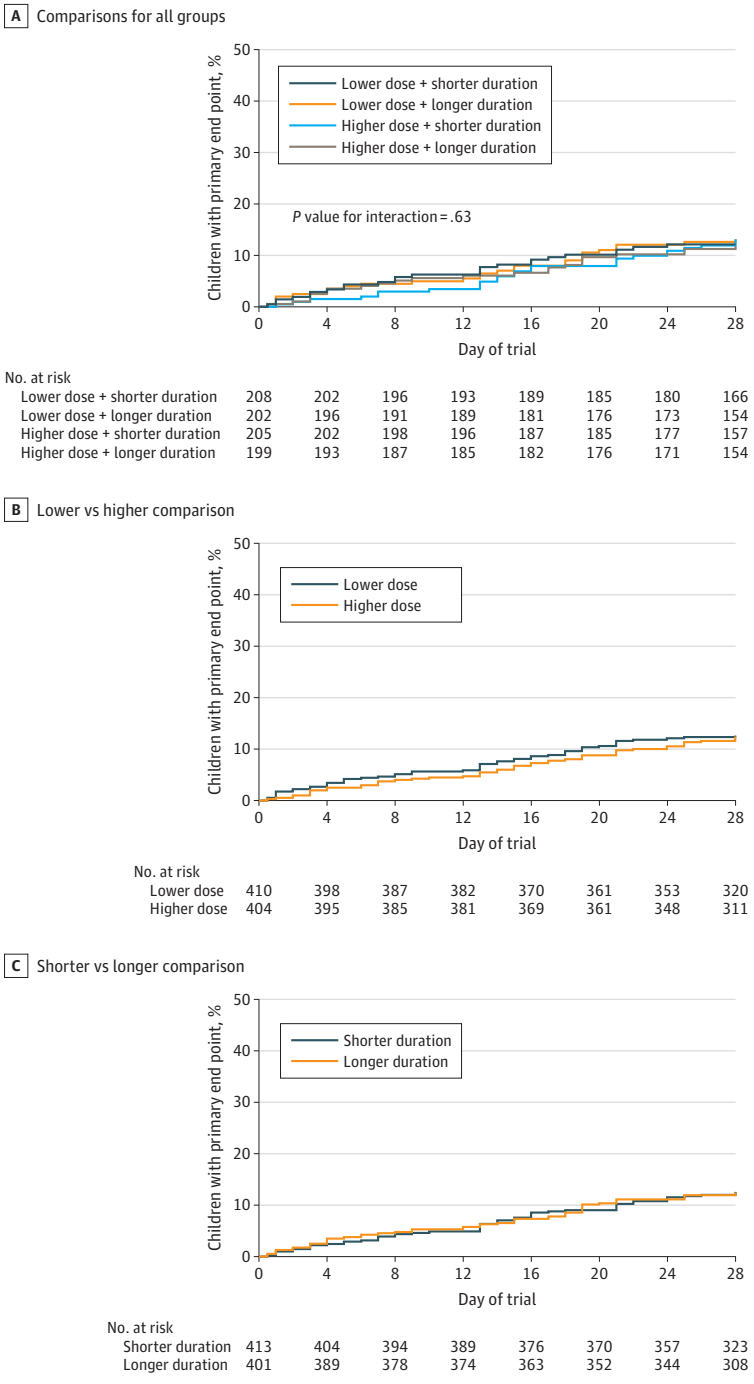
Prespecified sensitivity analyses included the following: (1) re-treatment regardless of reason or indication; (2) re-treatment specifically for CAP or chest infection; and (3) for duration, considering only re-treatments after 3 days from randomization. To provide support that a null result was not due to the inclusion of children with mild infection less likely to benefit from antibiotics, another prespecified analysis was limited to children with at least 2 abnormal physiological parameters at enrollment, considered the *severe* group (eMethods 7 in Supplement 2). In addition, 2 post hoc analyses were undertaken: (1) ontreatment analysis with nonadherence defined as taking less than 80% of the trial medication (all trial medication including placebo and active drug only) (eMethods 8 in Supplement 2); and (2) subgroup analysis of children who had not received antibiotics in the hospital (most discharged immediately from the ED) and those who had received up to 48 hours of β-lactam treatment in the hospital before enrollment (eMethods 9 in Supplement 2).

Analyses of secondary end points were not adjusted for multiple comparisons. Because of the potential for type 1 error due to multiple comparisons, findings for secondary end points and analyses should be interpreted as exploratory. Binary outcomes were compared between groups using the χ^2 or Fisher exact test and logistic regression. Ordered outcomes were compared using rank tests. Duration of CAP symptoms was analyzed using time-to-event methods, restricted to children with the particular symptom at enrollment, until the first day the symptom was reported as absent. For all Cox models, the proportional hazards assumption was tested on the basis of Schoenfeld residuals. In none of these tests was the proportionality assumption violated. For secondary end points, all significance tests were performed under the standard null hypothesis of no difference.

Analyses of primary and secondary end points were to be based on observed data only taking into account information across all visits, with multiple imputation to be considered if data were missing for more than 10% of participants.

Data were analyzed using Stata software, version 15 (StataCorp). Differences in the primary end point are presented with 1-sided 95% CIs for the noninferiority analyses, and differences in secondary end points are presented with 2-sided 95% CIs. All statistical tests had a significance threshold of .05. See Supplement 3 for the statistical analysis plan.

Figure 2. Kaplan-Meier Curves Indicating Time to Experiencing the Primary End Point



The primary end point is clinically indicated treatment with systemic antibiotics (other than trial medication) for a respiratory tract infection within 4 weeks of randomization. Median observation time was not reported since more than 75% of participants were observed for the entire 28-day period. Lower dose indicates 35 to 50 mg/kg/d; higher dose, 70 to 90 mg/kg/d; shorter duration, 3-day course; longer duration, 7-day course.

A, No. (%) with primary end point by day 28: lower + shorter, 25 (12.1 [90% CI, 8.9-16.4]); lower + longer, 26 (13.1 [90% CI, 9.7-17.7]); higher + shorter, 26 (13.1 [90% CI, 9.6-17.6]); and higher + longer, 23 (11.8 [90% CI, 8.5-16.2]).

B, No. (%) with primary end point by day 28: lower, 51 (12.6 [90% CI, 10.1-15.6]); higher, 49 (12.4 [90% CI, 10.0-15.5]). Difference, 0.2% (upper bound of 1-sided 95% CI, 4.0%).

C, No. (%) with primary end point by day 28: shorter, 51 (12.5 [90% CI, 10.1-15.5]); longer, 49 (12.5 [90% CI, 10.0-15.5]). Difference, 0.1% (upper bound of 1-sided 95% CI, 3.9%).

The data and safety monitoring committee provided oversight of the study and reviewed unblinded data 3 times during the trial.

Results

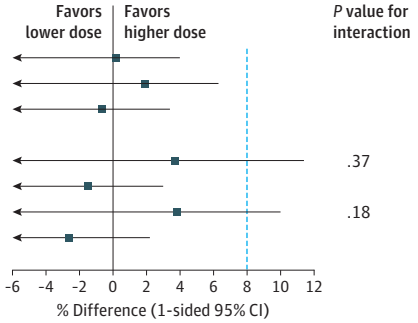
Between February 1, 2017, and April 23, 2019, 2642 children were assessed for eligibility, and 824 were randomized (**Figure 1**). Ten children received no trial medication and were excluded from the analysis, resulting in an analysis population of 814.

Of these, 421 (52%) children were male, 393 were female (48%), and median (IQR) age was 2.5 years (1.6-3.7) (**Table 1**). At presentation, 441 (54%) were febrile, 578 (71%) had tachycardia, and 528 (65%) had tachypnea. At randomization, 591 (73%) children were discharged directly from the ED, and 223 (27%) had an inpatient stay of less than 48 hours (eFigure 1, eTable 3, and eTable 4 in Supplement 2).

Figure 3. Noninferiority Sensitivity and Subgroup Analyses for the Primary End Point for the Amoxicillin Dose and Dose Duration Randomizations

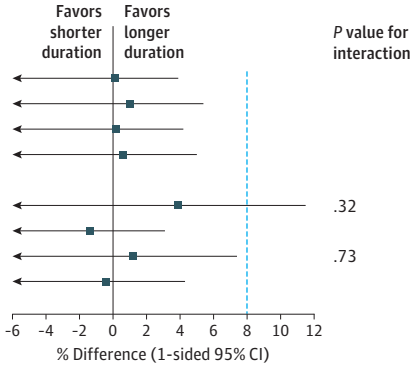
A Re-treatment by dose comparisons

End point	No. with re-treatment by day 28/total (%)		Difference (1-sided 95% CI)	P value for interaction
	Lower dose	Higher dose		
Primary end point, primary analysis	51/410 (12.6)	49/404 (12.4)	0.2 (-100.0 to 4.0)	
All systemic antibacterial re-treatments	74/410 (18.3)	65/404 (16.4)	1.9 (-100.0 to 6.3)	
Re-treatment due to CAP or chest infection	37/410 (9.1)	39/404 (9.8)	-0.7 (-100.0 to 3.4)	
Primary end point subgroups				
Prior inpatient antibiotics	16/107 (15.3)	13/116 (11.5)	3.7 (-100.0 to 11.4)	.37
No prior inpatient antibiotics	35/303 (11.7)	36/288 (12.8)	-1.5 (-100.0 to 3.0)	
Severe CAP	31/180 (17.3)	25/188 (13.5)	3.8 (-100.0 to 10.0)	.18
Nonsevere CAP	20/230 (8.9)	24/216 (11.5)	-2.6 (-100.0 to 2.2)	



B Re-treatment by duration comparisons

End point	No. with re-treatment by day 28/total (%)		Difference (1-sided 95% CI)	P value for interaction
	Shorter duration	Longer duration		
Primary end point, primary analysis	51/413 (12.5)	49/401 (12.5)	0.1 (-100.0 to 3.9)	
All systemic antibacterial re-treatments	73/413 (17.9)	66/401 (16.8)	1.0 (-100.0 to 5.4)	
Re-treatment due to CAP or chest infection	39/413 (9.5)	37/401 (9.4)	0.2 (-100.0 to 4.2)	
Re-treatment after day 3	46/413 (11.3)	42/401 (10.7)	0.6 (-100.0 to 5.0)	
Primary end point subgroups				
Prior inpatient antibiotics	17/114 (15.2)	12/109 (11.3)	3.9 (-100.0 to 11.5)	.32
No prior inpatient antibiotics	34/299 (11.5)	37/292 (12.9)	-1.4 (-100.0 to 3.1)	
Severe CAP	28/177 (16)	28/191 (14.8)	1.2 (-100.0 to 7.4)	.73
Nonsevere CAP	23/236 (9.9)	21/210 (10.4)	-0.4 (-100.0 to 4.3)	



The primary analysis and 3 prespecified analyses are shown for both randomizations including all systemic antibacterial re-treatments, only re-treatments for community-acquired pneumonia (CAP) or chest infection, and by severe CAP subgroups. In addition, a post hoc subgroup analysis by prior inpatient antibiotic exposure is shown. A sensitivity analysis including only re-treatments after day 3 is shown for the duration randomization. One-sided 95% CIs are shown with the lower bound extending to −100%. The blue dashed vertical line at 8% indicates the noninferiority margin.

Two hundred eighteen (98%) children who were inpatients and 24 (4%) who were discharged directly from the ED had received β-lactam antibiotics (100% treated for <48 hours and 185 (76%) <24 hours; eTable 5 in Supplement 2).

Follow-up data were available for 757 (93%) participants at day 3, 716 (88%) at day 7, 676 (83%) at day 14, and 619 (76%) at day 21. Final 28-day follow-up was face to face for 484 (59%) participants, and 158 (19%) families were contacted by telephone. Including additional information from family physicians regarding any subsequent antibiotic prescriptions (n = 147), the primary end point was evaluable for 789 (97%) children, with the remaining 25 providing data up to the point of last contact.

Primary Outcome

For the primary outcome, 139 children received nontrial systemic antibiotic treatment by day 28, with criteria for the primary end point met in 100 (12.5% [90% CI, 10.7% to 14.6%]) (**Figure 2**A; eTable 6, eTable 7, and eTable 8 in Supplement 2). There was no significant interaction between randomized factorial groups (P = .63; Figure 2A). The proportions meeting the primary end point were 12.6% (51/410) in the lower-dose group vs 12.4% (49/404) in the higher-dose group (difference, 0.2% [1-sided 95% CI, -∞ to 4.0%]; Figure 2B), and 12.5% (51/413) in the shorter-duration group vs 12.5% (49/401) in the longer-duration group (difference, 0.1% [1-sided 95% CI, -∞ to 3.9%]; Figure 2C). Both comparisons satisfied the noninferiority criterion (**Figure 3**). There were no significant interactions between use of antibiotics in the preceding 48 hours and either dose (P = .46) or duration randomizations (P = .59) (eFigure 2 in Supplement 2).

For the prespecified subgroup analysis among children with severe CAP, the primary end point occurred in 31/180 (17.3%) in the lower-dose group vs 25/188 (13.5%) in the higher-dose group (difference, 3.8% [1-sided 95% CI, -∞ to 10%]; P value for interaction, .18) and in 28/177 (16.0%) in the 3-day group vs 28/191 (14.8%) in the 7-day group (difference, 1.2% [1-sided 95% CI, -∞ to 7.4%]; P value for interaction, .73) (Figure 3).

Post hoc ontreatment analysis of 693 children who took 80% or more doses showed noninferiority for lower dose (lower vs higher, 9.5% vs 10.2%; difference, -0.7% [1-sided 95% CI, -∞ to 3.1%]) and shorter duration (shorter vs longer, 10.5% vs 9.2%; difference, 1.3% [1-sided 95% CI, -∞ to 5.1%]) (eFigure 3 and eFigure 4 in Supplement 2). In addition, in the subgroup of 591 children without prior inpatient antibiotics, the primary end point occurred in 11.7% in the lower-dose

Table 2. *Streptococcus pneumoniae* and Antimicrobial Resistance on Day 28 in Lower (35-50 mg/kg per Day) and Higher (70-90 mg/kg per Day) Dose and Shorter (3-Day) and Longer (7-Day) Duration Groups

Outcome	Amoxicillin dose				Amoxicillin duration			
	35-50 mg/kg per Day (n = 410)	70-90 mg/kg per Day (n = 404)	Difference, % (95% CI)	*P* value	3 Days (n = 413)	7 Days (n = 401)	Difference, % (95% CI)	*P* value
Culture sample available	224/410 (55)	213/404 (53)	2 (-5 to 9)	.58	205/413 (50)	232/401 (58)	-8 (-15 to -1)	.02
Streptococcus pneumoniae colonization	66/224 (29)	63/213 (30)	0 (-9 to 8)	.98	65/205 (32)	64/232 (28)	4 (-4 to 13)	.35
Penicillin MIC, mg/L								
0.016	18 (27)	10 (16)			15 (23)	13 (20)		
0.032	35 (53)	44 (70)			36 (55)	43 (67)		
0.064	1 (2)	0			0	1 (2)		
0.125	4 (6)	1 (2)		.49	3 (5)	2 (3)		.56
0.25	6 (9)	5 (8)			8 (12)	3 (5)		
0.5	0	1 (2)			1 (2)	0		
1	2 (3)	1 (2)			1 (2)	2 (3)		
2	0	1 (2)			1 (2)	0		
Penicillin nonsusceptibility[a]								
Including all samples	12/224 (5)	9/213 (4)	1 (-3 to 5)	.58	14/205 (7)	7/232 (3)	4 (-0 to 8)	.06
In positive samples	12/66 (18)	9/63 (14)	4 (-9 to 17)	.55	14/65 (22)	7/64 (11)	11 (-2 to 23)	.10
Amoxicillin MIC								
0.016	42 (64)	43 (68)			40 (62)	45 (70)		
0.032	14 (21)	11 (17)			12 (18)	13 (20)		
0.064	4 (6)	5 (8)			7 (11)	2 (3)		
0.125	2 (3)	0		.61	1 (2)	1 (2)		.21
0.25	2 (3)	2 (3)			3 (5)	1 (2)		
0.5	0	0			0	0		
1	2 (3)	1 (2)			1 (2)	2 (3)		
2	0	1 (2)			1 (2)	0		
Amoxicillin resistance/ nonsusceptibility[b]								
a) including all samples	2/224 (1)	2/213 (1)	0 (-2 to 2)	>.99	2/205 (1)	2/232 (1)	0 (-2 to 2)	>.99
b) in positive samples	2/66 (3)	2/63 (3)	0 (-6 to 6)	>.99	2/65 (3)	2/64 (3)	0 (-6 to 6)	>.99

Abbreviation: MIC, minimal inhibitory concentration.

[a] Break points for penicillin MIC: less than or equal to 0.064 mg/L indicates sensitive, 0.125 to 2 mg/L indicates nonsusceptible, and greater than 2 mg/L indicates resistant.

[b] Break points for amoxicillin MIC: less than or equal to 0.5 mg/L indicates sensitive, greater than 0.5 to 1 mg/L indicates nonsusceptible, and greaterh than 1 mg/L indicates resistant. The data stratified by randomization groups can be found in eTable 11 in Supplement2.

group vs 12.8% in the higher-dose group (difference, -1.5% [1-sided 95% CI, -∞ to 3.0%]) and in 11.5% in the shorter-duration group vs 12.9% in the longer-duration group (difference, -1.4% [1-sided 95% CI, -∞ to 3.1%]). Among the 223 children enrolled following inpatient antibiotic treatment, the corresponding rates were 15.3% in the lower-dose group vs 11.5% in the higher-dose group (difference, 3.7% [1-sided 95% CI, -∞ to 11.4%]) and 15.2% in the shorter-duration group vs 11.3% in the longer-duration group (difference, 3.9% [1-sided 95% CI, -∞ to 11.5%]) (eFigure 5, eFigure 6, eFigure 7, and eFigure 8 in Supplement 2); neither comparison met the noninferiority criterion. Post hoc interaction tests for these subgroups were not statistically significant (P = .37 with dose randomization; P = .32 with duration randomization).

Secondary Outcomes

Resolution of vomiting, fever, fast breathing, wheezing, interference with normal activity, reduced appetite, and phlegm production was not significantly different between groups by dose or duration. Cough persisted for longer in the shorter- vs longer-duration groups (median, 12 days vs 10 days; hazard ratio 1.2 [90% CI, 1.0 to 1.4]; P = .04), as did sleep disturbed by cough (median, 4 days vs 4 days; hazard ratio 1.2 [90% CI, 1.0 to 1.3]; P = .03; eFigure 9 and eFigure 11 in Supplement 2). There was no significant association between dose or duration of amoxicillin and severity of cough symptoms (eFigure 10 and eFigure 12 in Supplement 2).

A baseline nasopharyngeal sample was obtained from 647 participants, of which 272 (42%) were colonized by *S pneumoniae* with penicillin nonsusceptibility identified in 46 (16.9%) samples. At the final visit, 437 children provided a sample, of which 129 (29.5%) were positive for *S pneumoniae,* and penicillin nonsusceptibility was identified in 21 samples. No penicillin-resistant pneumococci were identified, and there was no significant difference in day 28 pneumococcal carriage or penicillin nonsusceptibility according to the dose or duration of amoxicillin (**Table 2**; eTable 11, eTable 12, eTable 13, and eTable 14 in Supplement 2).

Table 3. Adherence and Adverse Events in Lower (35-50 mg/kg per Day) and Higher (70-90 mg/kg per Day) Dose and Shorter (3-Day) and Longer (7-Day) Duration Groups

Outcome	Amoxicillin dose				Amoxicillin duration			
	35-50 mg/kg per Day (n = 410)	70-90 mg/kg per Day (n = 404)	Difference, % (95% CI)	*P* value	3 Days (n = 413)[a]	7 Days (n = 401)[a]	Difference, % (95% CI)	*P* value
Adherence: complete course taken								
All treatment[a]	355 (87)	366 (91)	-4 (-8 to -0)	.07	358 (87)	363 (91)	-4 (-8 to 1)	.09
Active treatment only[b]	383 (93)	384 (95)	-2 (-5 to 2)	.32	404 (98)	363 (91)	7 (4 to 10)	<.001
Adherence: all doses taken and all volumes as prescribed								
All treatment[b]	306 (75)	309 (76)	-2 (-8 to 4)	.54	300 (73)	315 (79)	-6 (-12 to -0)	.05
Active treatment only[c]	352 (86)	350 (87)	-1 (-6 to 4)	.75	387 (94)	315 (79)	15 (11 to 20)	<.001
Clinical possibly drug-related adverse events post enrollment								
Diarrhea	168 (42)	177 (45)	-4 (-10 to 3)	.31	187 (46)	158 (41)	6 (-1 to 12)	.11
Oral thrush	27 (7)	30 (8)	-1 (-5 to 3)	.60	25 (6)	32 (8)	-2 (-6 to 2)	.26
Rash	94 (23)	99 (25)	-2 (-8 to 4)	.52	87 (22)	106 (27)	-6 (-12 to -0)	.06
Serious adverse event, any[d]	23 (6)	20 (5)	1 (-2 to 4)	.67	25 (6)	18 (4)	2 (-2 to 5)	.32

[a] Courses were considered complete when trial drug was taken on all 7 days.

[b] Including nonadherence to placebo.

[c] Ignoring nonadherence to placebo.

[d] No participant had more than 1 serious adverse event, all serious adverse events were hospitalizations (most for respiratory distress), no deaths. The data stratified by randomization groups can be found in eTable 10 in Supplement 2.

Adverse Events

Of potentially amoxicillin-related clinical adverse events, diarrhea was reported in 345 (44%) children after baseline, skin rash in 193 (24%), and oral thrush in 57 (7%). Rash occurred in 106 (27%) children allocated to longer treatment compared with 87 (22%) children allocated to shorter treatment (**Table 3**; eTable 9 in Supplement 2). Active trial medication was discontinued early by 47 (6%) participants, while 112 (14%) took fewer doses or a lower volume than prescribed (Table 3; eTable 9 in Supplement 2). The main reasons for early discontinuation were clinical deterioration (n = 23), gagging or spitting out (n = 7), adverse events (n = 6), and clinical improvement (n = 3). Children randomized to 3 days of amoxicillin were more likely to complete their full treatment course compared with those randomized to a 7-day course (98% vs 91%).

In total, 43 (5%) children experienced a serious adverse event; all were hospitalizations, and most (37 [86%]) were due to respiratory illness (Table 3; and eTable 9 in Supplement 2). One serious adverse event (hospital admission for intravenous treatment because of vomiting on day 2 in a patient randomized to the higher-dose, shorter-duration group) was classified as related to trial medication. There were no deaths.

Discussion

In this pragmatic trial that evaluated dose and duration of amoxicillin for treatment of childhood CAP on discharge from the ED or an inpatient ward, antibiotic re-treatment rates for respiratory tract infection within 4 weeks were noninferior among those randomized to lower- vs higher-dose amoxicillin and among those randomized to a 3-day vs a 7-day course of treatment.

Noninferiority was confirmed in all prespecified sensitivity analyses. For the prespecified subgroup of children with severe disease at baseline, the CI was within the noninferiority margin for the duration comparison; however, for the dose comparison, it did not meet the noninferiority criterion, although the test for interaction by CAP severity at baseline was not statistically significant. The results were consistent with noninferiority in all post hoc ontreatment analyses, including only children taking more than 80% of the trial drug. In a post hoc subgroup analysis separating children discharged from the ED and those requiring inpatient hospitalization, the CI was within the noninferiority margin only for the larger ED group; it did not meet the noninferiority criterion for the children discharged after inpatient treatment, although the test for interaction by previous receipt of antibiotics were not statistically significant.

Few trials have compared different durations of the same antibiotic for treatment of CAP in adults or children, and none to our knowledge have compared both dose and duration in the same trial for childhood CAP.[15,22-28] The recently completed Canadian SAFER trial comparing 5-day with 10-day high-dose oral amoxicillin treatment for childhood CAP on discharge from the ED found comparable clinical cure rates in both groups (89% in the 5-day group and 84% in 10-day group) at 2 to 3 weeks.[27] Similarly, 3-day β-lactam therapy was recently reported to be noninferior to 8-day treatment in adults hospitalized with CAP in non-critical care wards.[28] As in this trial, re-treatment with nontrial antibiotics was part of the composite primary end point in the SAFER trial and provides a reasonable and important end point for high-resource settings where mortality and critical illness from childhood CAP are low.[29] Re-treatment rates in both the current trial and the SAFER trial are similar to the 10% to 11% previously observed for amoxicillin-treated lower respiratory tract infection in UK general practice.[27,30,31]

In this trial, amoxicillin was prescribed in 2 instead of 3 divided daily doses, an approach endorsed by patient representatives in the design phase and consistent with international guidance.[11,32-34] The trial findings suggest that a lower total

daily amoxicillin dose may be used in twice-daily dosing regimens, especially when prevalence of penicillin-resistant pneumococci is low. Observations of saturability of amoxicillin gut absorption limiting the achievement of desired amoxicillin exposure when using high oral doses at low administration frequency require further investigation.[35]

Limitations

This trial has several limitations. First, it is not possible to unequivocally identify children likely to benefit from antibiotics. Biomarkers and chest radiographs have been shown to have questionable discriminatory ability and are discouraged by some guidelines.[8-12] Although children with a mixed picture of CAP and obstructive airway disease were included, those with wheezing but without clinical signs of CAP were not included, and only 16% of children received bronchodilators or steroids compared with the 48% bronchodilator use observed in the most recent UK pediatric pneumonia audit.[36] Children commonly show a mixed pattern of disease (bacterial, viral with or without airway obstruction), and some antibiotic re-treatment may have been for self-limiting disease unlikely to respond to antibiotics.

Second, the trial findings do not inform total treatment duration for children initially admitted to the hospital. Optimal total treatment duration may differ for children requiring prolonged intravenous treatment as inpatients. Only 13% of children receiving inpatient treatment in this trial received antibiotics intravenously, consistent with UK recommendations.[12]

Third, the trial was not powered to investigate noninferiority of lower dose and shorter duration of home-based oral amoxicillin treatment in the subgroup of children discharged after an inpatient stay, and the tests for interaction may have been similarly underpowered.

Fourth, these findings should not be considered generalizable to children with very severe disease, including those with underlying comorbidities who may benefit from higher dose or longer treatment.

Conclusions

Among children with CAP discharged from an ED or hospital ward (within 48 hours), low-dose outpatient oral amoxicillin was noninferior to high dose, and 3-day duration was noninferior to 7 days, with regard to need for further antibiotic re-treatment. However, disease severity, treatment setting, prior antibiotics, and acceptability of the noninferiority margin require consideration when interpreting the findings.

ARTICLE INFORMATION

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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

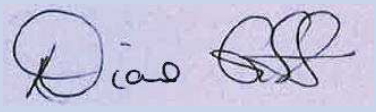
Version: Version 4.0
Date: 4 December 2018

MRC CTU at UCL ID: CAP-IT
ISRCTN #: ISRCTN76888927

EUDRACT #: 2016-000809-36
CTA #: 00316/0246/001-0006
REC #: 16/LO/0831

Authorised by:
Name: Professor Mike Sharland
Role: Chief Investigator

Name: Professor Di Gibb
Role: Programme Lead



GENERAL INFORMATION

This document was constructed using the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL) Protocol Template Version 4.0. The MRC CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. This document describes the CAP-IT trial, coordinated by the MRC CTU at UCL, and provides information about procedures for entering patients/participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact CAP-IT Trial Manager, MRC CTU at UCL, London, to confirm they have the most up-to-date version. MRC CTU at UCL may be referred to as MRC CTU throughout this document.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996 fourth revision, the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act 2018 (DPA number: Z6364106), the EU Regulation General Data Protection Regulations 2016/679/ EC (GDPR) and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

SPONSOR

UCL is the trial Sponsor and has delegated responsibility for the overall management of the CAP-IT trial to the MRC CTU at UCL. Queries relating to UCL sponsorship of this trial should be addressed to Professor Max Parmar, MRC CTU at UCL Director, Institute of Clinical Trials and Methodology, MRC CTU at UCL, 2nd Floor, 90 High Holborn, London, WC1V 6LJ.

FUNDING

Funding is provided by the National Institute of Health Research (NIHR), Health Technology Assessment (HTA) Programme, Antimicrobial Resistance Themed Call via grant number 13/88/11 and therefore receives support from the NIHR Clinical Research Network (NIHR CRN).

AUTHORISATIONS AND APPROVALS

This trial has been peer reviewed and scientifically approved by the NIHR HTA and is part of the NIHR Clinical Research Network (CRN) portfolio.

TRIAL REGISTRATION

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN76888927.

RANDOMISATIONS

Randomisation will be done by taking the next sequentially numbered blinded treatment kit from the PED or WARD supply (depending on which group the patient is joining). Kits must be stored separately for the PED and WARD groups. Each kit will have a unique number which should be entered onto the trial register and the database.

SAE REPORTING

Within 24 hours of becoming aware of an SAE, please transfer a completed SAE form to the MRC CTU at UCL via secure email to **mrcctu.capit@ucl.ac.uk**

TRIAL ADMINISTRATION

Please direct all queries to the Trial Manager at the MRC CTU in the first instance; clinical queries will be passed to the Chief Investigator and/or Trial Physician via the Trial Manager.

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Mandy Wan, Paediatric Clinical Trials Pharmacist	NIHR Clinical Research Network: Children Pharmacy Department
Professor Nigel Klein, Microbiome Study	Institute of Child Health, University College London

For full details of all trial committees, please see Appendix III

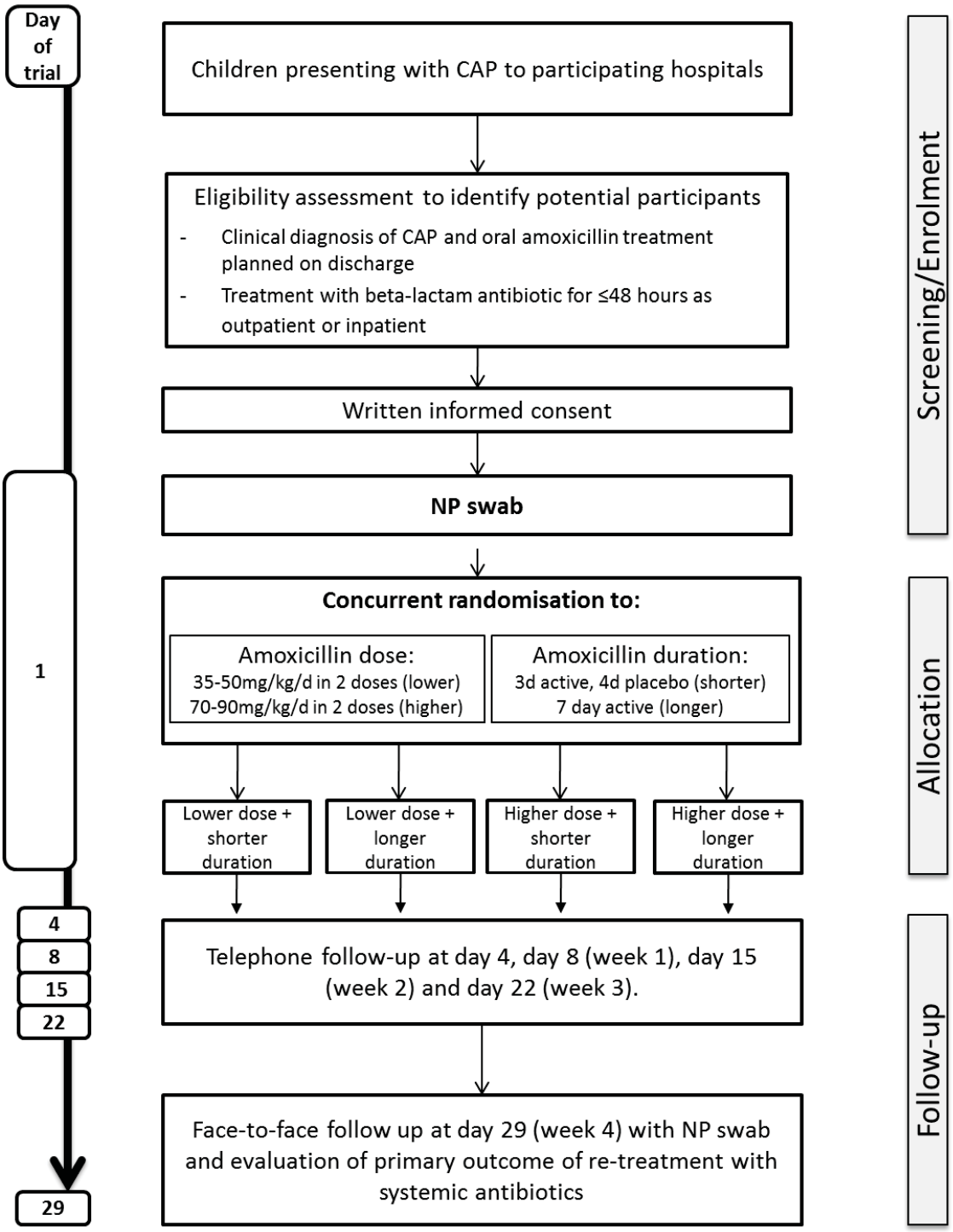
SUMMARY OF TRIAL

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)
Version	V3.4
Date	14 November 2018
UCL ID	16/0172
ISRCTN #	ISRCTN76888927
EudraCT #	2016-000809-36
CTA #	00316/0246/001-0006
MREC #	16/LO/0831
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	CAP-IT aims to recruit 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 amoxicillin. Children may have received up to 48 hours of beta-lactam antibiotics prior to randomisation, including any outpatient treatment. Children will be recruited into two groups: 1. PED Group: children who are recruited in the Paediatric Emergency Department (PED) 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 home 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.
Setting	CAP-IT aims to recruit children presenting to PEDs or PAUs or admitted to inpatient wards in the UK and Ireland.
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.

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	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
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	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 Measures	Severity and duration of parent-reported CAP symptoms; specified clinical adverse events (including thrush, skin rashes and diarrhoea); 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
Sponsor	University College London
Funder	NIHR HTA
Chief Investigators	Professor Mike Sharland/ Professor Diana Gibb
Trial Physician	Dr Julia Bielicki
Senior Statistician	Professor David Dunn

TRIAL SCHEMA

Figure 1. Trial schema



TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule – PED GROUP

	ASSESSMENTS Face-to-face ■ Telephone □ Face-to-face or Telephone ▒	DAYS IN TRIAL						
		Randomisation **d1**	**d4**	Week 1 **d8-10**	Week 2 **d15-17**	Week 3 **d22-24**	Week 4 **d29-31**	**Any acute event**
PED group	**Trial participation**							
	Parent/Guardian information sheet	X						
	Informed consent	X						
	Drug supply dispensing	X						
	Adherence review[a]		X	X				(X)[b]
	Adherence review (returned unused medication)						X	
	Clinical assessment							
	Medical history[c]	X						
	Physical examination[d]	X					X[d]	X[e]
	Symptom review[a]	X	X	X	X	X	X	X
	EQ-5D[f]	X	X	X			X	(X)
	Use of health services[a]		X		X	X	X	X
	Laboratory assessment							
	Nasopharyngeal swab[gh]	X					X	(X)
	Haematology[i]	(X)					(X)	(X)
	Biochemistry[j]	(X)					(X)	(X)
	Virology[k]	(X)					(X)	(X)
	Radiological assessment							
	Chest X-ray	(X)						(X)
	Parent-completed diary							
	Symptom diary[l]		X	X	X			
	Sub-studies							
	Stool sample	X[m]		X			X	

(X) indicates tests that may be done if the child's condition requires it or allows it, but are not mandatory.

Additional explanatory notes for investigations

a. Nurse administered questionnaire based on the CAP-IT symptom diary.
b. If acute event takes place during first 8 days after randomisation.
c. Includes review and duration of symptoms (cough, temperature and respiratory symptoms), documentation of any underlying diseases and antibiotic exposure within the last 3 months.
d. Includes weight and vital parameters (respiratory and heart rate, temperature and oxygen saturation). For the final study visit if no CAP symptoms are present, a limited physical exam can be done by the study nurse.
e. If clinically reviewed by the trial team.
f. Modified EQ-5D (wellbeing questionnaire) to be completed by parents at baseline, then with the nurse at day 4, day 8, day 29 and if an acute event takes place.
g. A nasopharyngeal swab should be collected prior to the child starting antibiotic treatment, at week 4 and if an acute event takes place. Please refer to the CAP-IT sample collection manual for details of collection and storage.
h. If parents give optional consent for future use of samples and genetic research the NP swab will be divided into STGG and RNALater samples. If consent is not given the NP swab will be transferred into the STGG sample only.
i. If available, Haemoglobin, Platelet count, Leukocyte count, Neutrophil count, Lymphocyte count.
j. If available, C-reactive protein, procalcitonin, urea, creatinine and electrolytes.
k. If available, rapid testing for RSV and Influenza A/B (any method).
l. To be completed by parents/guardians daily for 2 weeks. The symptom diary will also include questions relating to adherence to trial drug and the use of health services.

Substudy

m. Sample should be collected before randomisation or within 12 hours after randomisation. Please refer to the CAP-IT sample collection manual for details of collection and postage.

Table 2: Trial Assessment Schedule – WARD GROUP

	ASSESSMENTS Face to face ■ Telephone □ Face-to-face or Telephone		DAYS IN TRIAL						
		Pre-randomisation **≤48h before randomisation**	Randomisation **d1**	**d4**	Week 1 **d8-10**	Week 2 **d15-17**	Week 3 **d22-24**	Week 4 **d29-31**	**Any acute event**
WARD group	**Trial participation**								
	Parent/Guardian information sheet	X	X						
	Informed consent[a]		X						
	Drug supply dispensing		X						
	Adherence review[b]			X	X				(X)[c]
	Adherence review (returned unused medication)							X	
	Clinical assessment								
	Medical history[d]	(X)	X						
	Physical examination[e]	(X)	X					X[e]	X[f]
	Symptom review[b]	(X)	X	X	X	X	X	X	X
	Use of health services[b]		X[g]		X	X	X	X	X
	EQ-5D[h]		X	X	X			X	X
	Laboratory assessment								
	Nasopharyngeal swab[ij]	(X)	X					X	(X)
	Haematology[k]	(X)	(X)					(X)	(X)
	Biochemistry[l]	(X)	(X)					(X)	(X)
	Virology[m]	(X)	(X)					(X)	(X)
	Radiological assessment								
	Chest X-ray	(X)	(X)						(X)
	Parent-completed diary								
	Symptom diary[n]			X	X	X			
	Sub-study								
	Stool sample	X[o]	X		X			X	

(X) indicates tests that may be done if the child's condition requires it or allows it, but are not mandatory.

Additional explanatory notes for investigations

a. Deferred consent can be sought for storage of the pre-antibiotic treatment nasopharyngeal swab, if taken.
b. Nurse administered questionnaire based on the CAP-IT symptom diary.
c. If acute event takes place during first 8 days after randomisation.
d. Includes review and duration of symptoms (cough, temperature and respiratory symptoms), documentation of any underlying diseases and antibiotic exposure within the last 3 months.
e. Includes weight and vital parameters (respiratory and heart rate, temperature and oxygen saturation). For the final study visit if no CAP symptoms are present, a limited physical exam can be done by the study nurse.
f. If clinically reviewed by the trial team.
g. Data collection on healthcare use during hospitalisation from medical record including record of antibiotic and other supportive treatment up to the time of randomisation.
h. Modified EQ-5D (wellbeing questionnaire) to be complete by parents at baseline, then with the nurse at day 4, day 8, day 29 and if an acute event takes place.
i. A nasopharyngeal swab will be collected at randomisation and, if possible, prior to the child receiving antibiotic treatment. Deferred written informed consent will be sought for samples collected prior to formal enrolment in CAP-IT. Please refer to section 3.2 in the protocol for more details. A nasopharyngeal swab will also be collected at week 4 and if an acute event takes place. Please refer to the CAP-IT sample collection manual for details of collection and storage.
j. If parents give optional consent for future genetic research the NP swab will be divided into STGG and RNALater samples. If consent is not given the NP swab will be put into the STGG sample only.
k. If available, Haemoglobin, Platelet count, Leukocyte count, Neutrophil count, Lymphocyte count.
l. If available, C-reactive protein, procalcitonin, urea, creatinine and electrolytes.
m. If available, rapid testing for RSV and Influenza A/B (any method).
n. To be completed by parents/guardians daily for 2 weeks. The symptom diary will also include questions relating to adherence to trial drug and the use of health services.

Substudy

o. Sample should be collected as soon as possible after initiation of antibiotics. Please refer to the CAP-IT sample collection manual for details of collection and storage.

CONTENTS

ABBREVIATIONS

Abbreviation	Expansion
A&E	Accident and Emergency
AE	Adverse event
AMR	Antimicrobial Resistance
AR	Adverse reaction
bid/bd	Twice a day
BNF	British National Formulary
BNFc	British National Formulary for Children
BSAC	British Society of Antimicrobial Chemotherapy
BTS	British Thoracic Society
CAP	Community Acquired Pneumonia
CF	Consent Form
CI	Chief Investigator
CI	Confidence interval
CRF	Case Report Form
CRN	Clinical Research Network
CRP	C-reactive protein
CTA	Clinical Trials Authorisation
CTIMP	Clinical trial of an investigational medicinal product
CTU	Clinical Trials Unit
DPA	(UK) Data Protection Act
DSUR	Developmental Safety Update Report
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EudraCT	European Union Drug Regulatory Agency Clinical Trial

Abbreviation	Expansion
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HE	Health economics
HRA	Health Research Authority
IB	Investigator Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
LRTI	Lower Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimal Inhibitory Concentration
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London
NHS	National Health Service
NHS-IC	National Health Service Information Centre
NIHR	National Institute for Health Research
NIHR CSP	National Institute for Health Research Co-ordinated System for gaining NHS Permission
OD	Once daily
PALS	Patient Advice and Liaison Services
PAU	Paediatric Assessment Unit

Abbreviation	Expansion
PCV	Pneumococcal Vaccination
PED	Paediatric Emergency Department
PERUKI	Paediatric Emergency Research in the United Kingdom & Ireland
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PKPD	Pharmacokinetic-pharmacodynamics
po	by mouth
PSI	Pneumonia Severity Index
QMAG	Quality Management Advisory Group
QoL	Quality of life
QP	Qualified Person
R1	CAP-IT Randomisation 1: high vs low dose
R2	CAP-IT Randomisation 2: short vs long duration
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGC	Research Governance Committee
RGF	Research Governance Framework (for Health and Social Care)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard operating procedure
SPC	Summary of Product Characteristics

Abbreviation	Expansion
SSG	Scientific Strategy Group
SSI	Site-specific information
SUSAR	Suspected unexpected serious adverse reaction
TDS	thrice daily
T>MIC	Time spent over minimum inhibitory concentration
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
WHO	World Health Organization

1 BACKGROUND

1.1 COMMUNITY ACQUIRED PNEUMONIA (CAP) IN CHILDREN

1.1.1 EPIDEMIOLOGY

Antibiotics are amongst the most commonly used medicines in children.(1, 2) Annually, just under 50% of children younger than 2 years of age and one third of children over 3 years of age receive an antibiotic prescription across the UK, Netherlands and Italy.(2) Acute respiratory infections, including lower respiratory tract infections (LRTI) and community-acquired pneumonia (CAP), are common reasons for childhood healthcare consultations and are by far the most common indications for antibiotic use in children seen in primary care and in emergency departments.(3-5)

Streptococcus pneumoniae is the bacterial pathogen most commonly implicated in childhood CAP and other paediatric acute respiratory tract infections, even in settings with routine pneumococcal vaccination (PCV).(6-9) In the UK, PCV-7 was introduced in 2006 and PCV-13 in 2010, covering 13 *S. pneumoniae* serotypes with a very high uptake of almost 95% in young children.(10, 11) However, this has not been accompanied by decreased admissions rate due to CAP in young children, as perhaps would be expected based on the observed impact on invasive pneumococcal disease.(12-15)

1.1.2 ANTIBIOTIC USE AND HEALTH CARE UTILIZATION

In the US, antibiotics are prescribed at one in five paediatric ambulatory visits and 70% of these prescriptions are for respiratory conditions.(5) Up to 40% of preschool children consult in primary care for acute respiratory symptoms, which result in an antibiotic prescription in around 30%.(4, 16) A third of PED medical visits are due to respiratory symptoms, fever or cough and 7-15% of these children will be diagnosed with CAP.(17, 18) Overall, on average, one in three children <5 years of age and 1 in 5 children aged 5 to 18 years seen in the emergency department with acute respiratory infections will receive antibiotics.(19)

In the UK, both PED visits (around 1.34 million by children 1-4 years of age in 2012-13, according to Hospital Episode Statistics) and admissions of children with respiratory complaints have increased over the course of the last decade, mostly in preschool children, perhaps partly because of direct consultations in the PED bypassing primary care.(14, 17, 20, 21) Reflecting its on-going importance in the UK, 62% of antibiotic prescriptions for community-acquired infections in hospitalised 1-5 years olds are for CAP.(22) Early antibiotic treatment of lower respiratory tract infection has been suggested to reduce the need for hospitalisation.(23-25)

1.1.3 COSTS

More than 11,000 children <15 years of age were admitted in England with a diagnosis of bacterial pneumonia in 2008, and almost 9000 1-4 year-old inpatients with non-influenza pneumonia alone were recorded in 2012-13.(15, 20) In the early 2000s the estimated healthcare cost of childhood pneumonia in England was £6.3–£8.2 million per year.(26) For children initially treated IV, total societal costs for each hospitalisation in the UK were calculated as £1569 ± 1301.(27) This amounts to £17.3 million yearly when assuming around 11,000 CAP hospitalisations per annum.

1.2 CHALLENGES IN THE MANAGEMENT OF CHILDHOOD CAP

1.2.1 DIAGNOSING BACTERIAL CAP

Bacterial CAP is a differential diagnosis in any child presenting with fever and a combination of respiratory signs and symptoms, a raised age-adjusted respiratory rate and focal chest signs.(18, 28-30) When the listed features are seen in a child with an unwell appearance as judged by the evaluating physician, the likelihood of bacterial CAP requiring antibiotics is high.(18, 31) Wheezing is negatively associated with radiographic pneumonia and detection of bacteria.(28, 32)

No gold standard laboratory, microbiological or radiological tests reliably distinguishing bacterial from viral CAP exist.(33) Poor inter-observer agreement on CXR findings has cast doubt on their utility for identifying CAP of likely bacterial aetiology.(34-36) Microbiological tests such as sputum culture are either of little diagnostic value or cannot be obtained from young children. The diagnosis and decision to treat therefore have to be made based primarily on clinical criteria across the whole clinical spectrum of CAP.(33) The diagnostic challenge is accentuated in secondary care, which compared with general practice, sees serious bacterial infections at a higher rate.(37, 38)

1.2.2 ASSESSING SEVERITY OF CHILDHOOD BACTERIAL CAP

Available validated predictive scoring systems for assessing CAP severity, such as the Pneumonia Severity Index (PSI) or the CURB-65 (confusion, uremia, respiratory rate, low blood pressure), are not applicable to children.(39, 40) Low oxygen saturation in room air has been identified as an important differentiating factor between non-severe and severe pneumonia.(41-43) Pneumonia mortality risk scores for children have been developed in low-resource settings, but do not differentiate between viral and bacterial pneumonia.(44, 45) Low oxygen saturations are included as one factor to be assessed in these scores.

1.2.3 ASSESSING EFFICACY OF ANTIBIOTIC TREATMENT

The assessment of treatment efficacy in childhood CAP is complex. Studies in which efficacy was assessed early in the treatment course have used lack of improvement or worsening of clinical symptoms and signs, such as respiratory rate and oxygen saturation, as key measures.(46) These criteria correspond to those which according to the British Thoracic Society (BTS) guideline should currently always trigger a review of patient progress in children treated with oral antibiotics for CAP.(33) Specifically the BTS guideline recommends review in the presence of the following features at 48 hours: 1) persistent high fever after 48 hours of treatment, 2) increasing or persistently increased effort of breathing, 3) persistent or increasing oxygen requirement to maintain saturations ≥92%.(33)

More recently data have reported that re-exposure to antibiotics after home antibiotic treatment for CAP is around 15% for amoxicillin during a period of up to 28 days after initiation of treatment.(47) Symptoms of childhood CAP are known to be very worrying to parents, who often hold beliefs that are likely to result in a wish for their coughing and/or feverish child to receive antibiotics.(48-50) Only 50% of children show recovery from symptoms of acute respiratory illness by day 9-10, and a 90% recovery rate is observed approximately 3.5 weeks after symptom onset.(16, 51, 52) Given that symptoms may be one major trigger for retreatment, it is likely that retreatment is a relatively frequent feature of childhood CAP. Consequently, the measurement of re-exposure to antibiotics at up to 4 weeks after treatment represents an important effectiveness outcome, and has been used in trials carried out in well-resourced settings.(51, 53)

1.3 AMR IN THE CONTEXT OF CHILDHOOD CAP

1.3.1 EPIDEMIOLOGY

Rates of *S. pneumoniae* resistance in the UK are relatively low, reported to be around 15% for respiratory samples (mainly from adults) and 4-6% for blood culture isolates.(54) Higher-level resistance (with Minimal Inhibitory Concentration (MIC) >2µg/mL) has not been observed in blood culture isolates and was found in <1% of respiratory *S. pneumoniae* isolates in the UK since 2010.(54) As opposed to low levels of antimicrobial resistance (AMR) in *S. pneumoniae*, some worrying trends are observed in resistance to gut bacteria.(55) This situation will be exacerbated in a setting where antibiotics are used injudiciously.(55)

1.3.2 CURRENT IMPACT OF AMR ON CAP MANAGEMENT

The relationship between MIC and clinical outcome in CAP is complex. At present there are few data on the level of *S. pneumoniae* AMR that reduces amoxicillin effectiveness. MIC describes an *in vitro* phenomenon. The harmonisation of European breakpoints (i.e. the MIC at which an isolate is considered susceptible, intermediate or resistant) attempts to provide a link between clinical impact and in vitro observation of resistance.(56) So-called clinical breakpoints are determined based on a variety of data in addition to efficacy studies. This includes pharmacokinetic-pharmacodynamics (PKPD) data, which for penicillin usually take time above MIC of 40% as the key exposure measure.

Current European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for penicillin MIC in *S. pneumoniae* are S ≤0.06 / R >2mg/L.(56) These breakpoints are the same as those specified by the British Society of Antimicrobial Chemotherapy (BSAC). Treatment with amoxicillin is recommended even when disease is caused by penicillin-resistant pneumococci as long as there is no high-level penicillin resistance (penicillin MIC >=4ug/ml).(57, 58)

1.3.3 ANTIBIOTIC TREATMENT AND SELECTION OF RESISTANT BACTERIA

Children are known to have high rates of bacterial colonisation and this often represents an increased level of carriage of resistant organisms.(59, 60) These may then be passed on to others in the community, especially within a childcare setting.(61, 62) Interventions to maintain a low level of resistance amongst colonising bacteria may therefore have population implications.

The limited existing data on the specific impact of duration and dose of antibiotic treatment and subsequent colonisation with resistant bacteria *in vivo* suggest a complex and dynamic relationship.(59-70) Experimental models suggest that insufficiently high dosing could promote the selection of resistant pathogens, and that while most of the effect on bacterial load is achieved early on during antibiotic exposure, resistant isolates emerge after 4-5 days.(71-75) RCTs assessing the effect of antibiotic duration and dose have been called for as providing the strongest evidence for the relationship between antibiotic exposure and colonisation with resistant bacteria.(76) One such RCT found that higher dose, shorter duration amoxicillin therapy of childhood CAP led to less colonisation with resistant bacteria after 4 weeks as well as being associated with better adherence.(69) However, mathematical modelling indicates that this may come at the price of selecting isolates with higher levels of resistance and clinical efficacy was not addressed in the trial.(69, 75)

1.4 CURRENT MANAGEMENT RECOMMENDATIONS

1.4.1 ANTIBIOTIC SELECTION

Amoxicillin is the drug of choice for treatment of CAP in children according to the BTS guideline and several international guidelines.(33, 77-79) The key target for antibiotic treatment in childhood CAP is S. *pneumoniae*, which can be treated with amoxicillin in the absence of high-level penicillin resistance.

1.4.2 ANTIBIOTIC DOSING

Amoxicillin dose selection should be driven by PKPD considerations. The key PKPD parameter for beta-lactams (including amoxicillin) is time spent above MIC (T>MIC). The recommended T>MIC is 40-50% of the dosing interval, however the exact relationship between blood PK and concentrations of amoxicillin in the lungs is unclear.(77, 80) The half-life of oral amoxicillin is about 1.0-1.5 hours and, on this basis, a three times daily regimen has been widely recommended.(81) There are few data to inform whether three times daily dosing is likely to achieve PKPD parameters better than twice daily dosing. Indeed, available data suggest that twice daily dosing would be expected to achieve required T>MIC for total daily amoxicillin doses of 25-50mg/kg.(81) Together with a likely improvement in adherence with less frequent administration, twice daily dosing is widely recommended outside of the UK setting.(77-80) A Brazilian group was recently able to demonstrate non-inferiority of twice compared with thrice daily dosing of amoxicillin in childhood CAP.(82) Currently in the UK, the BNFc recommends amoxicillin 250mg TDS for children aged 1-5 years with CAP, resulting in approximately 40-80mg/kg/d amoxicillin dosing depending on the weight of the child.(83) It has recently been shown that such age-based amoxicillin dosing results in highly variable total daily doses and alternative strategies, such as weight-banded dosing, may be more appropriate.(84) Furthermore, much higher daily doses of amoxicillin up to 200mg/kg/d are recommended for the treatment of severe infections (BNFc).

1.4.3 ANTIBIOTIC DURATION

Several large RCTs have found shorter treatment courses in childhood CAP to be effective in the resource poor setting in terms of clinical cure, treatment failure and relapse rate.(85, 86) However, these trials were also recruiting children with wheezing and other symptoms considered indicative of a viral infection not requiring antibiotics. The generalisability of these findings to the UK has therefore been questioned.(33) The BTS recognises that there are no robust data to inform guidance on duration of antibiotic treatment in childhood CAP.(33) The BNFc recommends a 7-day course for treatment of childhood CAP, however European and WHO guidance suggests that a 3 to 5-day course be prescribed.(77, 83)

1.5 RELEVANT STUDIES

1.5.1 COMPLETED CLINICAL TRIALS AND SYSTEMATIC REVIEWS

Several current guidelines for the management of childhood CAP identify the lack of high-quality evidence from RCTs on which to base duration and dosing treatment strategies in children in the resource-rich setting.(33, 77, 78) A recent systematic review focussing on antibiotic treatment duration for a range of childhood infections proposes a minimal total duration of ≤ 7 days for moderate CAP (87), but indicates that robust evidence exists to support 3-day treatment in mild cases.

Most RCTs addressing antibiotic treatment strategies for childhood CAP have been carried out in resource-limited settings.(85, 86) Trials in resource-rich settings took place in countries with much

higher levels of penicillin non-susceptibility in *S. pneumoniae* than are seen in the UK.(53, 85) Older trials in the UK were relatively small and conducted when pneumococcal vaccination was not yet available. Thus trials up to now took place in settings with a different epidemiology of CAP, AMR and pneumococcal vaccine uptake/availability.

1.5.2 STUDIES UNDERWAY OR PLANNED

The University of Malaya is currently recruiting participants into a trial on the ideal duration of oral antibiotics in children with pneumonia (ClinicalTrials.gov: NCT02258763). This randomised placebo-controlled trial focuses on children hospitalised with CAP and aims to determine whether a 10-day course of antibiotic treatment with co-amoxiclav is superior to a 3-day course for clinical cure. The daily dose of co-amoxicillin will be 45mg/kg given in two doses. Resistance in bacterial isolates at 4 weeks after randomisation is included as a secondary endpoint. No other relevant studies underway or planned were identified.

A randomised controlled trial comparing 5 days with 10 days of treatment with high dose amoxicillin is currently recruiting at the Children's Hospital of Eastern Ontario, Canada (sponsor: Hamilton Health Sciences Corporation; ClinicalTrials.gov: NCT02380352). The daily dose of amoxicillin will be 90 mg/kg divided in three doses. The trial is recruiting children with mild CAP and evaluates the impact of duration of treatment on early clinical cure (resolution of tachypnoea, increased work of breathing and fever at 14 to 21 days). Microbiological endpoints are not included.

A similar duration comparison is being evaluated in the US in a multicentre trial aiming to recruit 400 children (ClinicalTrials.gov: NCT02891915). This study compares 5 days with 10 days of oral treatment of CAP with amoxicillin, amoxicillin-clavulanate or cefdinir. The amoxicillin dose is not specified. The primary outcome is the Desirability Of Outcome Ranking (DOOR) at day 8-10. The DOOR approach has recently been described as a potentially relevant outcome assessment in antibiotic trials and is, in essence, a ranked composite outcome.

1.6 RATIONALE FOR THE TRIAL

While there is clear agreement that amoxicillin should be used as first line in children requiring antibiotic treatment for CAP in the UK, there is insufficient data to inform the selection of dose and duration and the impact on resistance in key bacteria of specific amoxicillin dosing regimens is unknown.

Combined effectiveness and resistance outcome data according to dose and duration of antibiotics could inform antimicrobial stewardship strategies in the large group of children with a high likelihood of bacterial CAP targeted by CAP-IT. A better understanding of the relationship between dose and duration of antibiotic exposure and the development of resistance as well as the impact on clinical outcomes would make it possible to formulate improved evidence-based treatment recommendations for childhood CAP. CAP-IT will evaluate low dose + short duration, low dose + long duration, high dose + short duration, high dose + long duration to determine the most effective treatment. It is worth noting that all doses and durations are in the ranges recommended for childhood use of amoxicillin.

1.6.1 SERVICE EVALUATION

To inform the CAP-IT protocol, a service evaluation of paediatric CAP management was conducted in 26 emergency departments of the Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) network. Information on the management of 1-<6 year old children presenting with CAP, who were treated with antibiotics on attending the ED, was of interest regardless of whether these children were discharged or admitted to hospital. In total, 935 children with information on disposition after visiting the ED were included. From this feasibility work, several pieces of information relevant for the planning of CAP-IT emerge:

1) CAP remains a key infection in otherwise healthy young children seen in ED. On average, 5 such children eligible for the CAP-IT trial presented per site and week during early springtime. Of these, only 23% were admitted to hospital and the remainder were discharged with an antibiotic prescription. While the admission rate in our sample was high compared with overall admission rates of 8-10% in children presenting to UK EDs, it is clear that a minority of children with non-complicated CAP are managed as inpatients.
2) Of the admitted children, 38% were primarily managed in a short stay unit, where they received some antibiotic treatment in hospital, and only 14% were directly admitted to a paediatric ward. Overall, 71% of these children were hospitalised for a maximum of up to 2 days with even shorter hospital stays noted in the group admitted to a short stay unit. Thus while more severe clinical disease at baseline is associated with hospital admission, there is a spectrum of CAP with many admitted children showing similar features to those immediately discharge from the ED.
3) The general patterns of antibiotic use were similar between children discharged home after ED assessment and those admitted for a short period of 2 days or less, again suggesting that this group represents a continuous spectrum of CAP disease.
4) We confirmed that the total daily doses evaluated in CAP-IT all fall well into the range of doses currently being used for oral amoxicillin. In the feasibility survey, the observed total daily amoxicillin doses ranged from 20 mg/kg to 100 mg/kg in the same age group as is of interest for CAP-IT.

Evaluation of defined amoxicillin regimens for home-based treatment is of interest for admitted and immediately discharged children. CAP-IT will address the overall clinical question for how long and at what amoxicillin dose children with CAP discharged home from hospital should be treated.

The specific primary objectives of CAP-IT are:

1. To determine whether 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 treatments.
2. To determine whether 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..

The benefits of this trial will be:

- The development of an evidence-base for recommending amoxicillin treatment duration and dose that achieves resolution of symptoms of CAP while minimising the acquisition of resistant bacteria.
- A strengthened clinical trials network of PED, general paediatric and specialist paediatric infection networks relevant to the study of managing serious childhood bacterial infections.

2 SELECTION OF SITES/CLINICIANS

The trial Sponsor has overall responsibility for site and investigator selection.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

To participate in the CAP-IT trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been agreed by the CAP-IT Trial Management Group (TMG) and are defined below.

Recruitment of children will take place in large paediatric centres with designated PEDs that are part of the Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) network.

Those centres that meet the criteria will be issued with the CAP-IT master file documentation for their local approval and MRC CTU at UCL site accreditation documents. Centres must complete the CAP-IT accreditation documentation at the same time as applying for their local approval.

2.1.1 PI's Qualifications & Agreements

The Principal Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site. The PI should provide evidence of such qualifications through an up-to-date curriculum vitae and other relevant documentation requested by the Sponsor, the REC, and the regulatory authority.

The investigator should be thoroughly familiar with the appropriate use of the investigational product as described in the protocol, and in the SPC.

The investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of up-to-date GCP training should be accessible for all investigators.

The investigator/site should permit monitoring and auditing by the Sponsor, and inspection by regulatory authorities.

The investigator should maintain a delegation log of appropriately-qualified persons to whom the investigator has delegated significant trial-related duties.

The investigator should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.2 Adequate Resources

1. The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4. The investigator should ensure trained staff are available to recruit out-of-hours.

2.1.3 SITE ASSESSMENT

Each selected clinical trial site must complete the CAP-IT Accreditation documentation which includes the Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. A copy will be signed by the Principal Investigator at the site. In addition and in compliance with the principles of GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the MRC CTU at UCL. The MRC CTU at UCL must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Investigator Site File (ISF) at the site and also in the Trial Master File (TMF) at the MRC CTU at UCL.

MRC CTU will provide each site with full details of the essential documentation required prior to site activation. Only when all of the essential documents are in place will a site be activated to recruitment.

2.2 APPROVAL AND ACTIVATION

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating site principal investigators. Trial staff at the MRC CTU at UCL will perform this task; hence it is vital to receive full contact details for all investigators prior to their entering participants.

On receipt of all of the essential documents at the MRC CTU at UCL and completion of all appropriate training, written confirmation will be sent to the PI. The site pharmacist will also be informed of the site activation and an initial drug order will be dispatched to the named pharmacist in the accreditation documents.

1. The site should conduct the trial in compliance with the protocol as agreed by the Sponsor and by the regulatory authority, and which was given favourable opinion by the REC.

2. The PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the MRC CTU at UCL.

A list of activated sites may be obtained from the Trial Manager.

3 SELECTION OF PARTICIPANTS

CAP-IT aims to recruit children via 2 different pathways:

1. PED group: children who are recruited in the Paediatric Emergency Department (PED) or Paediatric Assessment Unit (PAU). Children in this group will be treated at home with amoxicillin without receiving any in-hospital antibiotics. These children will be entered into the trial either prior to receiving any antibiotic prescription OR after ≤48 hours uninterrupted oral beta-lactam treatment in the community.
2. WARD group: children who are recruited from in-hospital paediatric hospital wards or paediatric assessment units (PAUs) following in-hospital treatment with beta-lactam antibiotics. Children in this group will receive ≤48 hours total treatment with any beta-lactam antibiotic prior to entering the trial. Treatment may start in the community before in-hospital treatment, provided treatment is uninterrupted.

The eligibility criteria differ between the 2 pathways; therefore the consent process, inclusion/exclusion criteria and screening procedures are presented separately for the PED and WARD groups. Throughout this document, the term 'parent/guardian' will be used to denote the person with legal responsibility for the child.

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to randomising a participant.

Participating centres will be asked to keep anonymised screening logs of potentially eligible children presenting by either of the two pathways, including those who were not approached or for whom the parents/guardians did not consent to participate in the trial.

Children will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below. Eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team (a clinician or nurse who has been trained in study procedures and has been delegated the responsibility by the site PI) at each participating site before children are randomised into the study.

3.1 PED GROUP

Children in the PED group will be recruited from the PED or PAU. Children in this group will be treated at home with antibiotics and they will be entered into the trial prior to receiving any antibiotic prescription OR after ≤48 hours of antibiotic treatment in the community. CAP-IT study drug will be started on discharge.

3.1.1 CONSENT PROCESS

Written informed consent for the child to enter into the trial and be randomised must be obtained from a parent/guardian after explanation of the aims, methods, benefits and potential hazards of the trial and **before** any trial-specific procedures. Consent may only be obtained once eligibility has been confirmed.

It must be made completely and unambiguously clear that the parent/guardian of a child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child.

SIGNED CONSENT FORMS MUST BE KEPT BY THE INVESTIGATOR AND DOCUMENTED IN THE RELEVANT CRF AND A COPY GIVEN TO THE FAMILY. A LETTER SHOULD BE SENT TO THE GENERAL PRACTITIONER INFORMING HIM/HER OF THE TRIAL AND THE CHILD'S INVOLVEMENT IN IT.

3.1.2 INCLUSION CRITERIA

1. Age greater than 6 months and weighing 6 - 24kg
2. Clinical diagnosis of CAP at presentation to PED as defined by **all** of the following:
   - Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND
   - Temperature ≥38^{o}C measured by any method OR likely fever within 48 hours prior to presentation AND
   - Signs of laboured/difficult breathing or focal chest signs at presentation in the PED (i.e. one or more of the following):
     - Nasal flaring
     - Chest retractions
     - Abdominal breathing
     - Focal dullness to percussion
     - Focal reduced breath sounds
     - Crackles with asymmetry
     - Lobar pneumonia on chest X-ray (if obtained)
3. Prior antibiotic treatment:
   - Not on systemic antibiotic treatment at presentation OR
   - Treated in the community as an outpatient with uninterrupted oral beta-lactam antibiotics for ≤48 hours
4. Decision to treat with oral amoxicillin for CAP on discharge from hospital
5. Parent/guardian willing to accept all possible randomised allocations
6. Available for follow-up for the entire study period, parent/guardian willing to be contacted by telephone at day 4, weeks 1, 2 and 3, and attend a face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Informed consent form for trial participation signed by parent/guardian.

3.1.3 EXCLUSION CRITERIA

1. Severe underlying chronic disease with an increased risk of developing complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to amoxicillin
4. Need for systemic treatment with an antibiotic other than amoxicillin on discharge from hospital
5. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia (see Table 3)
7. Receipt of initial antibiotic treatment in hospital in PAU or on the ward*
8. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

*Child may be eligible for WARD group

Table 3: Features defined as indicating presence of complicated pneumonia

CAP COMPLICATED BY SEPSIS	CAP WITH SEVERE RESPIRATORY FAILURE	CAP WITH LOCAL COMPLICATIONS
Presence of shock requiring >20ml/kg fluid resuscitation Hypotension as defined by Advanced Paediatric Life Support/European Paediatric Life Support guidelines	Altered mental state (Glasgow Coma Score<14 or AVPU scale <A) Requirement for invasive ventilation or non-invasive ventilatory support	Empyema Pleural effusion Pneumothorax Pulmonary abscess Other complications involving the pleural or pulmonary space
Paediatric intensive care unit admission		

3.1.4 SCREENING PROCEDURES AND INVESTIGATIONS

Eligible children will be identified prior to being discharged from the PED with an antibiotic prescription. Written informed consent will be obtained during the PED consultation and prior to randomisation.

The following baseline information will be obtained:

1. Demographic information including gender and ethnicity (to ensure results are generalisable)
2. Medical history including review of symptoms (such as cough, fever and so on) and documentation of any underlying diseases.
3. Antibiotic exposure within the last 3 months including current antibiotic treatment, if applicable.
4. Physical examination including weight and vital parameters (temperature, respiratory rate, heart rate, oxygen saturation in room air)
5. Nasopharyngeal swab (collected at randomisation following informed consent). Every effort should be made to collect this sample however if for any reason it is not possible to obtain the nasopharyngeal swab, the child can still be included in the trial. If parents give optional consent for future use of samples and genetic research the NP swab will be divided into STGG and RNALater samples. If consent is not given the NP swab will be put into the STGG sample only.
6. Check of all inclusion and exclusion criteria
7. HR-QOL assessment

The following additional tests may be done at the local clinician's discretion if the child's condition requires it or allows it, but are not mandatory:

7. Haematology: haemoglobin, platelet count, leukocyte count, neutrophil count, lymphocyte count
8. Biochemistry: C-reactive protein, procalcitonin and electrolytes
9. Virology: rapid testing for RSV and Influenza A/B (any method)
10. Chest X-ray

The following will be obtained from children participating in the sub-study (and where additional consent is given):

11. Stool sample

Please refer to the CAP-IT sample collection manual for details of collection and storage of samples.

3.2 WARD GROUP

Eligible children for the WARD group should ideally be identified at the time of presentation, however, children in the WARD group will be randomised following in-hospital treatment with beta-lactam antibiotics. Children in this group will receive ≤48 hours' total treatment with any beta-lactam antibiotic prior to entering the trial. Treatment may start in the community before in-hospital treatment, provided treatment is uninterrupted.

3.2.1 NASOPHARYNGEAL SWAB

The nasopharyngeal swab will be obtained at randomisation. If at all possible, potentially eligible children presenting to the emergency department or assessment unit may have an additional nasopharyngeal swab taken *prior* to treatment with antibiotics. This will be prior to written informed consent having been obtained. In this case deferred written consent for the nasopharyngeal swab will be obtained when the parent/guardian consents to the main trial. If informed consent is refused, any study samples will be discarded and destroyed. Similarly, any samples from children who are subsequently found to be ineligible will be destroyed.

3.2.2 CONSENT PROCESS

Written informed consent for participation in the CAP-IT trial will be obtained when eligibility can be established at ≤48 hours after admission.

Written informed consent will be obtained from parents/guardians after explanation of the aims, methods, benefits and potential hazards of the trial and **before** randomisation. It must be made completely and unambiguously clear that the parent/guardian of a child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child.

Signed consent forms must be kept by the investigator and documented in the relevant CRF and a copy given to the family. A letter should be sent to the general practitioner informing him/her of the trial and the child's involvement in it.

3.2.3 INCLUSION CRITERIA

1. Age greater than 6 months and weighing 6 - 24kg.
2. Clinical diagnosis of CAP at presentation to hospital as defined by **all** of the following:
    - Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND;
    - Temperature ≥38^{o}C measured by any method OR likely fever within 48 hours prior to presentation AND;
    - Signs of laboured/difficult breathing or focal chest signs (i.e. one or more of the following):
        - Nasal flaring
        - Chest retractions
        - Abdominal breathing
        - Focal dullness to percussion
        - Focal reduced breath sounds
        - Crackles with asymmetry

- Lobar pneumonia on chest X-ray (if obtained)

3. Prior antibiotic treatment including doses administered in hospital (see **Figure 2**):
   - Treated in-hospital only with any oral or intravenous beta-lactam for ≤48 hours after admission
   - Treated initially in the community and subsequently in hospital with any oral or intravenous beta-lactam, without interruption, for ≤48 hours in total
4. Decision to further treat with oral amoxicillin for CAP on discharge from hospital
5. Child is considered fit for discharge at time of randomisation
6. Available for follow-up for the entire study period, parent/guardian willing to be contacted by telephone at weeks 1, 2 and 3 and attend face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Parent/guardian willing to accept all possible randomised allocations
8. Informed consent for trial participation signed by a parent/guardian

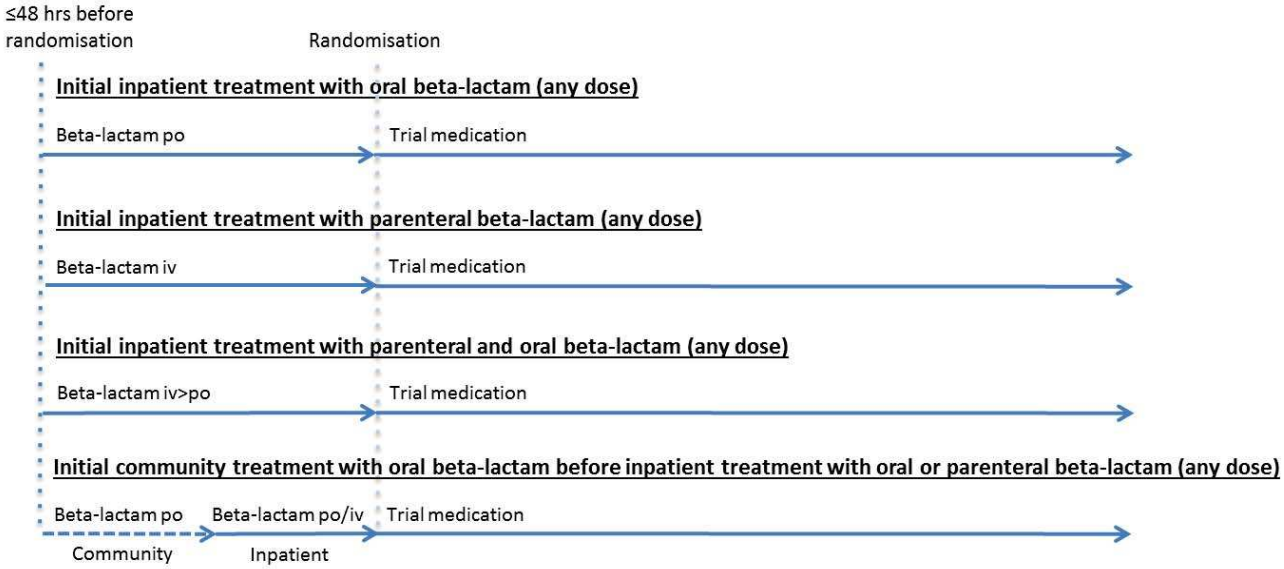


Figure 2. Acceptable antibiotic treatment during ≤48 hours prior to enrolment in WARD group

3.2.4 EXCLUSION CRITERIA

1. Severe underlying chronic disease with an increased risk of complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
5. Complicated pneumonia (see **Table 3**)
6. Receipt of antibiotic other than a beta-lactam during admission
7. If treated in the community prior to admission, receipt of a non-beta-lactam antibiotic in the community at presentation

8. Clinically relevant positive blood culture (i.e. positive blood culture and clinical decision to prolong intravenous treatment for more than 48 hours or inappropriate to switch to amoxicillin therapy)
9. Receipt of >48 hours oral or intravenous antibiotic treatment in total
10. Decision to treat with oral antibiotic other than amoxicillin on discharge from hospital
11. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

3.2.5 SCREENING PROCEDURES AND INVESTIGATIONS

The following baseline information should be obtained:

1. Demographic information including gender and ethnicity (to ensure results are generalisable)
2. Medical history including review and duration of symptoms (cough, temperature and respiratory symptoms), documentation of any underlying diseases and antibiotic exposure within the last 3 months
3. Physical examination including weight and vital parameters (temperature, respiratory rate, heart rate, oxygen saturation in room air)
4. Nasopharyngeal swab (see section 3.2.1)
5. Use of health services (data collection on healthcare use during hospitalisation from medical record including record of antibiotic and other supportive treatment up to the time of randomisation)
6. HR-QOL assessment
7. Check of all inclusion and exclusion criteria

The following additional tests may be done if the child's condition requires it or allows it, but are not mandatory:

8. Haematology, if available: haemoglobin, platelet count, leukocyte count, neutrophil count, lymphocyte count
9. Biochemistry, if available: C-reactive protein, procalcitonin and electrolytes
10. Virology, if available: rapid testing for RSV and Influenza A/B (any method)
11. Chest x-ray

The following will be obtained from children enrolled in sites participating in the sub-study (and where additional consent is given):

12. Stool sample

Please refer to the CAP-IT sample collection manual for details of collection and storage of samples.

4 REGISTRATION & RANDOMISATION

4.1 RANDOMISATION PRACTICALITIES

Treatments will be randomly assigned by taking the next sequentially numbered blinded treatment kits from the PED or WARD supply (depending on whether or not any non-trial antibiotic treatment for CAP is given in hospital).

Treatment kits for PED and WARD groups must be stored separately. Eligible children will be screened as described in **Section 3**. At randomisation the dose and duration interventions will be assigned simultaneously.

Patients will be registered via the online trial database accessible from the local clinical sites. This will be controlled through an authorised user name and password. Each treatment kit has a unique code and this will be entered into the trial database.

Further details on the process of randomisation can be found in **Section 9.1**.

A Trial Register will be provided to each site listing the trial ID numbers to be used. The date of randomisation and unique code of the allocated medicine should be added to the register.

4.2 CO-ENROLMENT GUIDELINES

Concurrent participation in any other clinical study of an investigational medicinal product is not allowed for the duration of the follow up period i.e. 28 days after randomisation. Participation in observational studies is acceptable in accordance with local guidelines.

5 TREATMENT OF PARTICIPANTS

5.1 INTRODUCTION

All participants will receive standard of care supportive treatment for CAP including oxygen supplementation and maintenance intravenous fluids or nasogastric fluids/feeds where necessary. The treating physician, parent/guardian and outcome assessors will be blinded to the allocated treatment. Study medication will be distributed from a dedicated pre-packaged and labelled supply of study drugs. These will be stored separately from routine clinic drug supplies in a designated section of the pharmacy or emergency department at the study sites.

5.2 TRIAL TREATMENTS

All children participating in CAP-IT will be receiving oral amoxicillin. Trial treatment should start on the day of randomisation. The 1st dose should be given prior to discharge where possible.

5.2.1 RANDOMISATION 1 (R1): DOSE OF ORAL AMOXICILLIN

Children will be randomised to receive either 35-50mg/kg/day or 70-90mg/kg/day. Dose randomisation will be achieved by using oral amoxicillin products of two different strengths, 125mg/5ml and 250mg/5ml oral amoxicillin suspension. This makes it possible to use the same absolute single doses (ml/dose) regardless of the target mg/kg per day dose. Relevant doses will be determined according to weight band (see **section 5.3**).

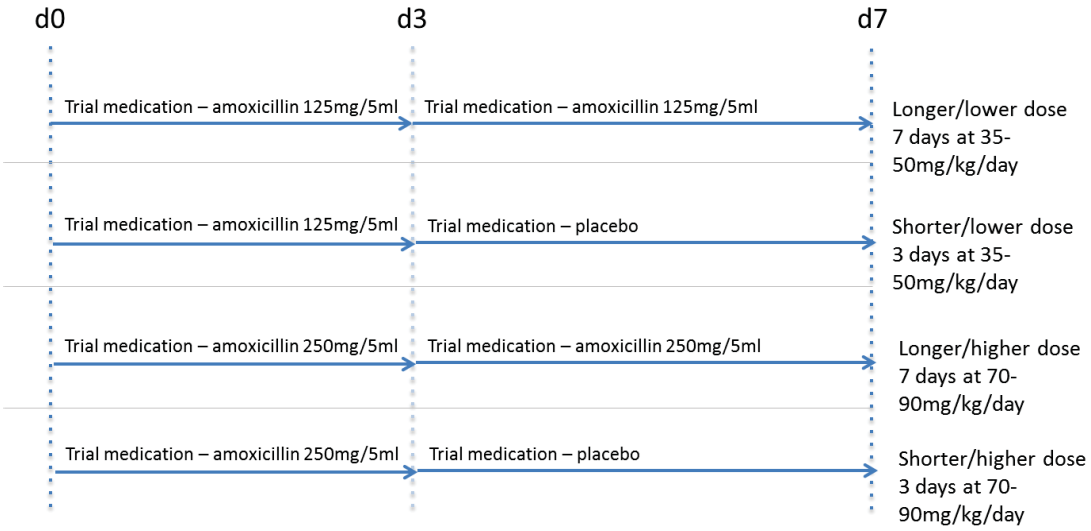
5.2.2 RANDOMISATION 2 (R2): DURATION OF ORAL AMOXICILLIN

Concurrently to R1, children will be randomised to receive either 3 days or 7 days of amoxicillin treatment. The use of placebo ensures parent and clinic staff blinding to amoxicillin treatment duration. Amoxicillin and matched placebo powder (to be reconstituted at the time of randomisation) will be used to prepare blinded packs. As it is difficult to exactly match antibiotic suspensions in taste for active and placebo drugs, one brand of amoxicillin will be used for all participating children for the first 3 days of treatment. This will be followed by a second bottle for days 4-7 containing either a second brand of amoxicillin or placebo. Both active drug and placebo will form a yellow-coloured similar tasting suspension. All parents will be instructed to expect some change in taste of the suspension after the first 3 days of treatment. Hence blinding to duration can be reliably maintained.

5.2.3 SUMMARY OF R1 AND R2

The factorial design described in **sections 5.2.1** and **5.2.2** will result in four treatment arms as shown in **Figure 3** below.

Figure 3. Treatment arms



5.3 PRODUCTS AND DOSING SCHEDULE

Amoxicillin oral suspension will be provided as trial supplies to be given orally twice daily. Dosing will be by weight band as shown in **Table 4**. The volume of suspension to be administered remains the same by weight band regardless of whether children have been randomised to the lower or the higher dose arm. All doses are within the recommended dose range for amoxicillin.

Body weight should be obtained on the day of presentation to PED by weighing children on an appropriate scale. Children should be weighed in light clothes, without shoes. Body weight reported by parents is not acceptable. If body weight could not be obtained during PED assessment for children in the WARD group, participants should be weighed during the second eligibility screen in the manner described. This weight should be used to determine the correct weight-band for the trial.

Table 4: Trial medication will be dosed according to body weight in kg by using the following dosing table:

WEIGHT BAND	WEIGHT RANGE	MLS PER DAY	MLS PER DOSE (BID)
1	<6.5kg	9	4.5
2	6.5-<8.5	12	6
3	8.5-<10.5	15	7.5
4	10.5-<13.5	19	9.5
5	13.5-<17kg	24	12
6	17-<21kg	30	15
7	21-24kg	33	16.5

The placebo suspension will be matched to the second amoxicillin suspension.

5.3.1 ADHERENCE AND ACCEPTABILITY

Amoxicillin is used widely in the UK for treatment of bacterial respiratory tract infections with extremely low rates of toxicity. Mild unwanted side-effects, including diarrhoea and thrush, have been reported.(88, 89) The importance of adherence should be reinforced at the time of dispensation of trial medication and during any subsequent contacts with the study team. Adherence will be assessed using the symptom diary, during week 1 telephone follow-up (see Table 1 & 2) and by review of unused medication at final follow-up.

Amoxicillin suspension is the most commonly used single antibiotic formulation for the treatment of children in the UK. Amoxicillin suspension has been reported to be acceptable to parents. While in this study the administration of relatively large volumes per single dose is required for older (and heavier) children, a twice daily dosing schedule will be used. This is known to improve compliance and make administration of antibiotics to schedule easier for parents.

5.4 DISPENSING

The trial medication will be stored separately from routine clinic drug supplies in a designated section of the pharmacy or other appropriate location, such as the emergency department, clinical research facility or ward at the study sites. Supplies for the PED and WARD groups must be kept separately. At randomisation, the next sequentially numbered blinded treatment kit from the PED or WARD supply should be selected, depending on which group the patient is joining.

The suspension can be reconstituted by the pharmacist, clinician or research nurse prior to dispensing to the parent/guardian. The parent/guardian will be provided with a supply of drug sufficient to last for the full 7 days of study medication.

Medication will be provided as a kit comprising 1 bottle of active amoxicillin (blinded to strength) and 2 bottles of amoxicillin/placebo. The bottles will be clearly labelled and colour-coded to indicate which should be used on days 1-3 and which should be used on days 4-7. However it is important that parents are provided with very clear guidance on this as well as an information sheet before the child is discharged. For children <13.5kg, the second bottle of amoxicillin/placebo will not be required and should be removed from the kit before dispensing to the parent/guardian.

Families will be requested to return all empty packages and any unused medication to the follow-up clinic at week 4. Any drug assigned to a child should on no account be used by anyone else.

All drugs dispensed and returned to the site should be documented on a treatment log. At each site, a named person (pharmacist or research nurse) will be required to maintain complete records of all study medication dispensed. The designated pharmacist/nurse will, on receipt of supplies prior to the start of the trial, conduct an inventory and complete a receipt.

5.5 ACCOUNTABILITY

Procedures for drug distribution, labelling, accountability and destruction will be detailed in the CAP-IT Pharmacy Manual of Operations. Drug accountability will be regularly monitored and the remaining stocks checked against the amounts dispensed. At the end of the study, all remaining

investigational drugs will be destroyed. CTU will monitor drug accountability centrally and during site visits.

5.6 DOSE MODIFICATIONS, INTERRUPTIONS AND DISCONTINUATIONS OF TRIAL TREATMENT

CAP-IT only involves amoxicillin, an active drug that would be routinely given to children with CAP. The doses given to the participants in all the study arms are within the internationally recommended amoxicillin dosing range (see **Section 5.3**).

5.6.1 DRUG SUBSTITUTION

In cases where there is an issue with tolerability of the trial medication resulting in recurrent spitting or gagging, in the first instance parents should be advised that trial medication can be taken with food and can be mixed with baby formula, milk, fruit juice, water or another cold drink to improve tolerability. If issues persist, trial medication may be switched to an alternative amoxicillin formulation or another antibiotic if the child is still assessed to be in need of continued treatment. This mirrors routine clinical practice, and the decision to continue antibiotic treatment is based on the assessment of the child. No additional relevant information is likely to be identified from unblinding.

Adverse events caused by drug toxicity leading to a treatment change are expected to be rare (see **below**). In the situation when a penicillin allergic reaction is suspected (e.g. typical, indicative skin rash) it would be customary to switch to an antibiotic of a different class. Substitution can be done without the need to unblind the treatment allocation. Children should remain in the study for follow-up and should continue to follow the assessment schedule.

5.6.2 OVERDOSE OF TRIAL MEDICATION

Parents/guardians of the children participating in the study should be counselled about the importance of taking the medications as prescribed. Although renal injury has been described in paediatric patients after accidental amoxicillin overdose, this has not been observed at doses below 250mg/kg/day, which is twice the highest daily dose in CAP-IT. Parents/guardians should contact the CAP-IT research team immediately if their child has been overdosed, to receive appropriate advice. Participants will then be managed on a case by case basis and toxicity will be managed in all randomised groups according to standard clinical practice.

5.6.3 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, parents/guardians are consenting, on behalf of their child, to trial treatment, trial follow-up and data collection. However, an individual child may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable toxicity or adverse event
- Any change in the child's condition that justifies the discontinuation or modification of the trial treatment in the clinician's opinion
- Use of a medication with a known major or moderate drug interaction with amoxicillin that is essential for the child's management
- Withdrawal of consent for treatment by the parent/guardian

As the child's participation in the trial is entirely voluntary, the parent/guardian may choose to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled. Although parents/guardians are not required to give a reason for discontinuing

their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

5.7 UNBLINDING

Situations necessitating unblinding are likely to be rare.

If they happen, severe allergic reactions (immediate type 1 reactions) are expected to occur early during amoxicillin exposure, when all randomised participants would be receiving active drug. Delayed drug reactions are generally mild and self-limiting and resolve with discontinuation of the drug. The onset of mild delayed reactions is frequent at 10-14 days after treatment exposure, i.e. after trial treatment has already been completed. Delayed drug reactions may occur earlier as a reaction to re-exposure (i.e. in children re-exposed to amoxicillin). In severe cases, immediate discontinuation and future avoidance of the suspected trigger is recommended. As all participants in CAP-IT will be exposed to amoxicillin, unblinding is unlikely to impact future management decisions in suspected penicillin allergic reactions. See **Section 5.6.1** for advice regarding drug substitution in such cases.

In situations where re-treatment becomes necessary, unblinding is unlikely to impact on the choice of antibiotic to be used therefore unblinding for this reason will not be necessary.

Emergency unblinding will only be necessary in situations of significant overdose of trial medication. Details of the volume ingested at which this will become necessary are specified on the CAP-IT website (www.capitstudy.org.uk). Emergency unblinding procedures can also be found there and in the CAP-IT Emergency Unblinding Procedures for Sites document.

5.8 NON-TRIAL TREATMENT

5.8.1 MEDICATIONS PERMITTED

All necessary concomitant medications are allowed. Parents will be asked to report the use of specified drugs, such as paracetamol, in the symptom diary. If a medication with a known major or moderate drug interaction with amoxicillin (see 5.8.2) is essential for a child's management and cannot be replaced by a drug that does not have an interaction with amoxicillin, then the trial medication should be stopped and the concomitant medication used (see **Section 6.8**).

5.8.2 MEDICATIONS NOT PERMITTED

Medications with known interactions with amoxicillin, which include allopurinol, methotrexate, mycophenolate and Vitamin K, are not used in otherwise healthy children in the target age group. In addition, amoxicillin may diminish the therapeutic effects of BCG and oral Typhoid Vaccine. These immunisations should be postponed until after completion of trial medication.

5.8.3 RE-TREATMENT WITH ANTIBIOTICS

In situations where re-treatment becomes necessary, the choice of antibiotic to be used will be left to the treating physician. This is likely to be either a repeat course of amoxicillin or a course of an alternative antibiotic.

6 ASSESSMENTS & FOLLOW-UP

6.1 TRIAL ASSESSMENT SCHEDULE

The frequency of follow-up visits and assessments are detailed in the Trial Assessment Schedule (see **page 9 - 12**). Separate tables are provided for the PED and WARD groups for clarity.

Trial visit and contact schedules will be prepared for each child at randomisation, and children should be followed on that same schedule, until the final follow-up visit, even if their trial medication is discontinued prematurely. The target dates for trial visits and contacts are determined by the date of randomisation and are not affected by subsequent events. The schedule defines visit dates (with windows) necessary for data collection.

Trial contacts are scheduled as follows:

- Telephone contact will be made by sites at day 4, day 8 (week 1), day 15 (week 2) and day 22 (week 3).
- A face-to face visit will be done at week 4 (within 2 days of day 29) for a final follow-up visit.
- During any acute events, the child can be seen face-to-face if attending the randomising centre. Otherwise, a telephone contact can be arranged.

6.1.1 TELEPHONE CONTACT

A review of clinical signs and symptoms must be performed at each telephone contact during follow-up. The following will be recorded:

- Standardised symptom checklist including review of cough, presence of rapid breathing, fever, general state and common known side effects of amoxicillin.
- Specified clinical adverse events since last protocol contact, including rashes and diarrhoea.
- Any acute illnesses requiring assessment by a healthcare provider since last protocol contact, including whether any antibiotic prescriptions were issued.
- Systemic antibiotic treatment since last protocol contact, including, as appropriate, adherence to CAP-IT treatment and whether any additional/new antibiotic prescriptions were issued.

6.1.2 FACE-TO-FACE VISITS (INCLUDING ACUTE EVENTS)

A review of clinical signs and symptoms must be performed at each face-to-face visit. The following will be recorded for all visits:

- Standardised symptom checklist including review of cough, presence of rapid breathing, fever and general state.
- Specified clinical adverse events since last protocol contact, including rashes and diarrhoea.
- Any acute illnesses requiring assessment by a healthcare provider since last protocol contact.
- Antibiotic treatment since last protocol contact, including, as appropriate, adherence to CAP-IT treatment and whether any additional/new antibiotic prescriptions were issued.
- A nasopharyngeal swab and saliva sample will be collected.

Should the patient have any signs or symptoms of CAP, the following will also be recorded:

- Relevant physical examination findings including vital parameters (respiratory rate, heart rate and oxygen saturation in room air).

At the final follow-up visit, parents/guardians will be asked to bring along all trial treatment bottles. These should be reviewed for adherence to treatment.

The week 4 visit will be scheduled in advance and parents/guardians will receive a reminder 3-4 days before the visit. Participants are expected to attend on the scheduled days and if not possible, every effort should be made to complete the study visit within 2 working days of the scheduled visit. If a scheduled visit or contact is missed without notice then the research team will endeavour to contact the parent/guardian by phone. If the final follow up is done by phone, the format of the visit will be the same as all other telephone follow up visits, as described in section 6.1.1.

To facilitate follow-up at week 4, a home visit can be arranged. Centres may choose to re-schedule visits or contacts to allow for public holidays or other unavoidable circumstances that affect the scheduled visit date, but the re-scheduled visit or contact should preferably be in the window period as detailed in the trial schema.

Parents/guardians will be given a card with the contact details for the trial research team at their site.

6.2 MICROBIOLOGICAL TESTS

A summary of the sample collection requirements are provided below however please refer to the CAP-IT sample collection manual for full details.

6.2.1 NASOPHARYNGEAL SWABS

Fine bore nasopharyngeal swabs will be collected at the following time-points in both the PED and WARD groups:

- At randomisation
- At week 4 follow-up visit (day 29)
- At any face-to-face review at participating centres that takes place as a result of any acute event (see **Section 6.6** for more details on acute events)

For WARD children, an additional swab should, if possible, be collected prior to antibiotic therapy has been started.

Nasopharyngeal swabs will be collected from all participants. Immediately after swabbing, the swabs will be kept cool (4-8^{o}C), and vortexed for 20-30 seconds at maximum speed before being frozen as soon as possible (no later than 4-6 hours) after the samples were obtained. Where sites are able to do this, the nasal swab will be cut in two and split between vials containing STGG (bacterial enrichment broth) and RNAlater (RNA preservation medium). The RNAlater sample should be kept in the refrigerator overnight, and then transferred ideally to -80°C for long-term storage (-20^{o}C is acceptable where no -80^{o}C freezer is available). These samples will be retained for future research and sent to the relevant central laboratory (Bristol) in batches on dry ice. Frozen STGG samples will be thawed and processed to identify *S. pneumoniae* using culture-based techniques; identification of changes in antibiotic resistance will use traditional minimum inhibitory concentration (MIC)-based techniques.

RNALater samples will be used for future exploration of gene expression and therefore should only be stored where consent for both future studies and genetic work has been given.

6.2.2 SALIVA SAMPLES (DELETED FROM PROTOCOL V 4.0 ONWARDS)

~~Saliva samples will be collected at the same points as nasopharyngeal swabs (see 6.2.1)~~

~~Saliva samples will be collected from all participants at sites that are able to use the sample kits provided. A foam swab will be placed into the child's mouth until it is saturated with saliva. The foam tip will then be immediately removed and placed in the barrel of a syringe to allow the saliva to be squeezed directly into a vial containing bacterial enrichment broth by applying pressure to the syringe plunger. Saliva samples will be kept cool (4-8°C), and vortexed for 20-30 seconds at maximum speed before being frozen as soon as possible (no later than 4-6 hours) after the samples were obtained. The saliva samples will be locally stored frozen, ideally at -80°C (-20°C is acceptable where no -80°C freezer is available), and sent to the relevant central laboratory (Bristol) in batches on dry ice. Frozen samples will be stored for use in future research.~~

6.2.3 ADDITIONAL MICROBIOLOGICAL TESTS (SUBSTUDY IN A SUBSET OF CHILDREN)

Stool samples will be collected at enrolment, after finishing the course of antibiotics and at final follow-up from 100 children at selected sites to allow for the evaluation of the impact of amoxicillin exposure on different microbial communities, including antibiotic resistance in the gastrointestinal commensal flora.

6.3 LABORATORY AND RADIOLOGICAL TESTS

There are no mandatory laboratory assessments beyond specific microbiological tests (see **Section 6.2**) and no mandatory radiological assessments for participants recruited into CAP-IT. However, results of the following should be recorded, if carried out as part of routine clinical care:

- Haematology: haemoglobin, platelets, white cell count, neutrophil and lymphocyte counts
- Biochemistry: CRP or other inflammatory markers (e.g. procalcitonin), Urea, Creatinine and electrolytes
- Virology: rapid testing for RSV and Influenza A/B (any method)
- Radiology: chest X-ray radiological report

6.4 ADHERENCE AND ACCEPTABILITY

All parents/guardians will be asked questions on adherence at each follow-up phone call and will be asked to return any unused medication at final follow-up. Parent/guardian responses to the adherence questions administered during telephone contact at week 1 follow-up will be related to parent/guardian records of administered doses in the symptom diary.

6.5 COSTS AND MEASURES OF QUALITY OF LIFE

Information on ongoing symptoms and time away from out-of-home child care/parent time off-work will be captured in the symptom diary and reviewed at each protocol contact. Data on all events and resources used among CAP-IT participants will be prospectively captured and will cover the use of medication and laboratory tests as well as hospital, primary care and community health services. Similarly, health outcomes in terms of duration of illness (or length of stay), relapse and mortality, will be collected.

Additionally for WARD group children, assessment will include information on healthcare services utilisation during the initial hospitalisation (admission and discharge dates, supportive and antibiotic treatment costs), but will otherwise use the same approach as described above.

Wellbeing questionnaires (EQ-5D adapted for use in the paediatric population) will be completed with parents at randomisation, on the telephone calls at days 4 and 8, at final follow-up and during any acute events. Outcomes for each dimension will be converted into a QoL score for each health outcome (treatment success, treatment failure resulting in re-treatment, and treatment failure resulting in re-admission). Information from the parent/guardian-completed symptom diary will augment this, as these will be completed daily as well as additional information collected weekly.

6.6 ACUTE EVENTS

Additional contacts may be necessary, for example if the child gets worse or develops potential adverse drug reactions or other clinical events. Parents/guardians will be encouraged to liaise with the study team whenever they are considering presenting their child for an acute assessment during the follow-up period of 28 days from randomisation.

Parents/guardians will be advised to seek immediate emergency assessment with a qualified healthcare provider, preferably at the recruiting centre emergency department, whenever they feel this is required.

During acute unscheduled medical assessment at recruiting centres, clinical staff will be requested to provide information on basic clinical findings including relevant examination findings and vital parameters. An additional nasopharyngeal swab and saliva sample will also be obtained. Medical judgement will be exercised in determining whether an event is an important medical event and might require special treatment or hospitalisation.

Following any acute unscheduled medical assessment, symptoms, health services utilisation and adherence (if appropriate) will be reviewed in the same way as during regular telephone contacts. Face-to-face visits will be arranged, if necessary, with the clinical team at the recruiting centre.

Please note that if any acute event meets the criteria for an SAE as defined in **Table 5** then an SAE form will be required. Refer to **Section 7** for further details.

6.7 DESCRIPTION OF PROCEDURES AND INSTRUMENTS

6.7.1 SYMPTOM DIARY

All parents/guardians will be provided with a diary to complete over the course of the follow-up period. This will be completed either in electronic or paper format and sites should follow

instructions from MRC CTU regarding which format to use. If parents consent to their email address and/or mobile phone number being stored in the study database they will receive reminders via email or text. The diary will include:

- Validated symptom record of child's cough, breathing, temperature and general state, and presence of specified clinical adverse events
- Record of administration of trial medication
- Record of use of health services:
  - Acute contacts with healthcare providers
  - Time away from routine childcare and parents'/guardians' work
  - Prescription and administration of additional antibiotic treatments
  - Administration of any anti-fever or anti-cough medication

Follow-up at day 4, day 8 (week 1), day 15 (week 2) and day 22 (week 3) will be done via a structured telephone call, with a question guide for CAP-IT research staff based on the symptom diary completed by parents/guardians.

We will also provide a picture diary for children, which will offer them the opportunity to document their participation by recording when they take their study medication and how they are feeling during the first 8 days in the trial. This diary can be offered to parents/guardians of children who are able and willing to complete the child diary but it is not mandatory.

6.7.2 PROCEDURES FOR ASSESSING ADDITIONAL ANTIBIOTIC TREATMENT

Information about all antibiotic prescriptions will be elicited at each scheduled contact with the trial team during the follow-up period. Parents/guardians will also be asked to complete the relevant section in the symptom diary to aid recall, and to invite any healthcare professionals involved in acute unscheduled assessments during the follow-up period to provide limited information about the outcome of these assessments. Information will be requested on any additional antibiotic treatment including type of antibiotic and duration of treatment. Additional antibiotic treatments will be recorded by the study team on the relevant form.

As part of the written informed consent for the CAP-IT study, parents/ guardians give consent for their child's GP to provide information on any antibiotic prescriptions during the planned 29 day duration of the study for that patient. Where a participant is lost to follow up, information on antibiotic prescriptions during this period will be elicited through contact with the participant's GP.

In the case of a parent/guardian's decision to withdraw from the study, parent/guardians will be asked whether they consent to further data collection through hospital notes and NHS records. If consent is given, information on antibiotic prescriptions during the planned 29 day duration of the study for that patient will be elicited through contact with the participant's GP.

6.7.3 PROCEDURES FOR ASSESSING SAFETY

The symptom diary will explicitly prompt for known clinical adverse effects of amoxicillin, primarily gastrointestinal symptoms and rash. Additional investigations may be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Pre-specified clinical adverse events will be recorded on the CRF. Serious adverse events will be defined according to GCP and reported to the MRC CTU within 24 hours of the investigator becoming aware of the event (see **Section 7**). Serious adverse events will be graded using the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table).

6.8 EARLY STOPPING OF TRIAL FOLLOW-UP

A parent/guardian who chooses to discontinue trial treatment for their child should be encouraged to follow the trial procedures and follow-up schedule. However, a decision to stop their child's participation early must be accepted. In this case, the CTU should be informed of this in writing using the appropriate form.

If follow-up is stopped early, the medical data collected during their participation in the trial will be kept and used in the analysis, as consent cannot be withdrawn for data already collected. Similarly, samples obtained prior to this time will be processed according to the protocol, unless the parent/guardian explicitly and unprompted requests otherwise. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should follow a discussion).

Prior to transferring to routine follow-up, the parent/guardian will be asked to have assessments performed as appropriate for a final study visit. They would be at liberty to refuse any or all individual components of the assessment.

Children who stop trial follow-up early will not be replaced in the trial.

6.9 LOSS TO FOLLOW-UP

For operational management at participating sites, a child will be classified as "lost to follow-up" only when three unsuccessful attempts have been made to contact the parent at each of the outstanding visits and when 2 scheduled end of study appointments have been missed. If an individual telephone follow-up visit is missed, the site team should continue to attempt to contact the parent via phone and/or email for all future visits, including the final face-to-face follow up. Home visits should be offered on a case by case basis as appropriate to minimise loss to follow-up. If it is evident that a face-to-face visit cannot be arranged during the designated time frame, every effort should be made to conduct telephone follow-up instead. If the final follow up is done by phone, the format of the visit will be the same as all other telephone follow up visits, as described in section 6.1.1.

6.10 COMPLETION OF PROTOCOL FOLLOW-UP

The trial will end after the last follow-up visit of the last randomised participant. Sites will be closed once data cleaning is completed and the regulatory authorities and ethics committee will be informed.

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in table 5.

Table 5: Definitions

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

7.1.1 MEDICINAL PRODUCTS

An investigational medicinal product is defined as the tested investigational medicinal product and the comparators used in the study. (EU guidance ENTR/CT 3, April 2006 revision).

Adverse reactions include any untoward or unintended response to drugs. Reactions to an trial medication or comparator should be reported appropriately.

7.1.2 ADVERSE EVENTS

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

7.1.3 EXEMPTED SERIOUS ADVERSE EVENTS

The following events, in the context of this trial, should not be considered as SAEs and are exempt from expedited reporting. Where applicable, they should be reported on the appropriate CRF:

- Pre-existing disease or a condition present before treatment that does not worsen
- Overdose of medication without signs or symptoms

7.2 INVESTIGATOR RESPONSIBILITIES

All non-serious AEs and ARs, whether expected or not, should be recorded in the child's medical notes and, if appropriate, reported in the clinical symptoms section of the appropriate CRF and data entered within the agreed timescale. All adverse events that lead to cessation of trial treatment should be recorded in the relevant section of the CRF. SAEs and SARs should be notified to the MRC CTU at UCL within 24 hours of the investigator becoming aware of the event.

7.2.1 INVESTIGATOR ASSESSMENT

7.2.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in **Table 5**. If the event is serious and not exempt from expedited reporting as detailed in **Section 7.1.3,** then an SAE Form must be completed and the MRC CTU at UCL notified within 24 hours.

7.2.1.B Severity or Grading of Adverse Events

The severity of all serious AEs and/or ARs in this trial should be graded using the toxicity grading in **Appendix II**.

7.2.1.C Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in **Table 6**. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 6: Assigning Type of SAE Through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Unrelated	There is no evidence of any causal relationship.	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment and drug is stopped or the dose modified, refer to **Section 5.6**.

7.2.1.D Expectedness

If there is at least a possible involvement of the trial treatment (or comparator), the investigator should make an initial assessment of the expectedness of the event, however the Sponsor has the final responsibility for determination of expectedness. An unexpected adverse reaction is one not previously reported in the current Summary of Product Characteristics (SPC) or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in **Table 5**. Please see Appendix I for a list of expected toxicities associated with amoxicillin. If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.2.1.E Notification

The MRC CTU at UCL should be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

Investigators should notify the MRC CTU at UCL of all SAEs, SARs and SUSARs occurring from the time of randomisation until the week 4 follow-up assessment. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system.

7.2.2 NOTIFICATION PROCEDURE

The SAE Form must be completed by the investigator (a clinician named on the Signature List and Delegation of Responsibilities Log who is responsible for the child's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed and signed by a member of the site trial team and faxed to MRC CTU at UCL. The responsible investigator should subsequently check the SAE Form, make changes as appropriate, sign and then re-fax to the MRC CTU at UCL as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting, the event, and why it is considered serious.

The SAE Form must be sent by fax or email to MRC CTU at UCL
Fax: +44 (0) 20 7670 4814; Email: **mrcctu.capit@ucl.ac.uk**

Follow-up of SAEs: children must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. A further SAE Form, indicated as 'Follow-up' should be completed and faxed to the MRC CTU at UCL as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The child must be identified by trial number, date of birth and initials only. The child's name should not be used on any correspondence and should be deleted from any test results.

Staff should follow their institution's procedure for local notification requirements.

7.3 MRC CTU AT UCL RESPONSIBILITIES

Medically-qualified staff at the MRC CTU at UCL and/or the Chief Investigator (or a medically-qualified delegate) will review all SAE reports received. In the case of disagreement with regards to the causality assessment, both opinions will be provided in any subsequent reports.

The MRC CTU at UCL is undertaking the duties of trial Sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the research ethics committees, as appropriate. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the MRC CTU at UCL becoming aware of the event; other SUSARs must be reported within 15 days.

The MRC CTU at UCL will also keep all investigators informed of any safety issues that arise during the course of the trial.

The MRC CTU at UCL, as Sponsor, will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to Competent Authorities (Regulatory Authority) and Ethics Committee.

The manufacturer of the placebo will be notified of any events, which may be attributed to the placebo.

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), Safety Management Plan and Monitoring Plan which will be separately reviewed by the Quality Management Advisory Group (QMAG).

8.2 CENTRAL MONITORING AT MRC CTU AT UCL

MRC CTU at UCL staff will review entered data for possible errors and missing data points.

Other essential trial issues, events and outputs will be detailed in the Monitoring Plan that is based on the trial-specific Risk Assessment.

8.3 ON-SITE MONITORING

The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring Plan. This plan will also detail the procedures for review and sign-off.

8.3.1 DIRECT ACCESS TO PARTICIPANT RECORDS

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Parents'/guardians' consent for this must be obtained.

8.3.2 CONFIDENTIALITY

The principles of the UK Data Protection Act (DPA) and GDPR will be followed.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Children will be allocated 1:1 to each of the two factorial randomisations, separately for the PED and WARD group. Randomisation lists will be computer-generated based on random permuted blocks, stratified by clinical site.

9.2 AIMS AND OBJECTIVES

CAP-IT will evaluate the efficacy, safety and effect on bacterial resistance of the duration and dose of amoxicillin treatment for young children with uncomplicated CAP.

The specific primary objectives are:

- To determine whether 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 treatments.
- To determine whether 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.

9.3 OUTCOME MEASURES

9.3.1 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.

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 or adverse reaction to trial medication, (c) parental preference, or (d) administrative error will not constitute a primary endpoint.

9.3.2 SECONDARY OUTCOME MEASURES

9.3.2A Morbidity:

- Severity and duration of parent/guardian-reported CAP symptoms.
- Specified clinical adverse events, including thrush, skin rashes and diarrhoea.

9.3.2B Microbiological:

- Phenotypic resistance to penicillin at week 4 measured in *S. pneumoniae* isolates colonising the nasopharynx.

9.3.2C Adherence:

- Adherence to trial drug.

9.4 SAMPLE SIZE

WARD and PED groups will be analysed jointly. The sample size is based on demonstrating non-inferiority for the primary efficacy endpoint (see **Section 9.3.1**) 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% (see **Section 1**). However, emerging data from the trial after the pilot phase suggest that the rate of the revised primary outcome (**Section 9.3.1**) is approximately 15%, without any clear difference between WARD and PED groups. Assuming a 15% event rate, 8% non-inferiority margin assessed against an upper 1-sided 95% CI, 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.

9.5 INTERIM MONITORING & ANALYSES

An IDMC Charter describes the membership of the Independent Data Monitoring Committee (IDMC), relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses. Formal statistical stopping rules will not be used in the trial although the IDMC Charter specifies guidelines for when the IDMC will alert the Trial Steering Committee (TSC) to the need to possibly modify the trial design. These guidelines will be conservative to guard against premature changes to the trial design from early inspection of the data.

9.6 ANALYSIS PLAN (BRIEF)

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

PED and WARD groups will be analysed jointly. The primary analysis will be modified intention-to-treat (mITT), including all participants who take at least one dose of trial medication, and analysing according to the group to which they were randomised. The primary endpoint will be analysed using time-to-event methods, controlling for previous antibiotic exposure. Multivariate analyses will be performed to test for potential interaction effects, in particular, dose*duration, dose*previous antibiotic exposure, and duration*previous antibiotic exposure. As tests for interaction are known to have low statistical power, these will be supplemented with visual inspection of appropriate cross-tabulations. Previous antibiotic exposure will be modelled both as a binary variable (yes/no) and as the time since first antibiotic prescription.

The primary analysis of the primary endpoint will include only those endpoints accepted by the ERC. However, sensitivity analyses will be performed: 1) including all systemic antibacterial treatments other than trial medication regardless of reason and indication; and 2) including only ERC-adjudicated clinically indicated systemic antibacterial treatment prescribed specifically for CAP (rather than any respiratory tract infection).

A subgroup analysis will consider the severity of CAP at presentation and repeat the main efficacy analysis 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 of viral aetiology.

Lower dose treatment and shorter duration will be will be considered “non-inferior” to higher dose and longer duration treatment, respectively, if the upper limit of the 1-sided 95% 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%. However, inference will be based primarily on point estimates and confidence intervals rather than the binary classification of a “non-inferior” or “not non-inferior” outcome.

For some secondary outcomes, including adverse events and resistance, on-treatment analyses will be performed as well as ITT analyses.

10 ANCILLARY STUDIES

10.1 IMPACT ON GASTROINTESTINAL MICROFLORA (SUB-STUDY)

For the analysis of the impact of amoxicillin on gastrointestinal microflora, a stool specimen will be collected in a subset of 100 children at selected sites and frozen. The day 0 sample will be collected before randomisation or in the first 12 hours after randomisation in children in the PED group and in the first 24 hours of hospitalisation in the WARD group, if possible, or as soon as possible after initiation of antibiotics. The day 8 and 29 samples can be taken at home using a custom-made collection kit, which has been evaluated by one of the co-applicants for the use in young children. Pre-addressed freepost envelopes will be provided for parents to send the samples directly to the central laboratory (Institute of Child Health, UCL) to be processed and stored.

10.2 DIARY METHODOLOGY (SUB-STUDY)

The more widespread use of the Internet and Web-based technologies suggests that Web-based questionnaires may be a reliable alternative to paper questionnaires in future studies. The method of data collection for parent reported information will be randomised at all sites. Parents will be asked to either complete the symptom diary online or on paper. Parents completing the paper diary will be asked to return it at the final study visit.

10.3 HEALTH-ECONOMIC ANALYSES (ANCILLARY STUDY)

Depending on the main trial results and further funding, a full health-economic analysis may be conducted. Monetary valuation of data on all relevant events and resources used for the treatment of CAP among participants will be conducted expressed as unit costs. The economic evaluation will adopt a health services perspective. Unit costs will be attached to resource use, using the best available estimates of long run marginal opportunity cost, to obtain a cost per participant over the period of follow-up.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the 1996 version of the Declaration of Helsinki.

It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 (The Medicines for Human Use [Clinical Trials] Regulations 2004) and subsequent amendments, the UK Data Protection Act 2018 (DPA number: Z5886415), the General Data Protection Regulation (GDPR) and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

11.1.2 SITE COMPLIANCE

The sites will comply with the above. An agreement will be in place between the site and the MRC CTU at UCL, setting out respective roles and responsibilities.

The site will inform the MRC CTU at UCL as soon as they are aware of a possible serious breach of compliance, so that the MRC CTU at UCL can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial

11.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 15 years after the end of the trial. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor, with suitable notice. The data may be subject to an audit by the competent authorities.

11.2 ETHICAL CONDUCT OF THE STUDY

11.2.1 ETHICAL CONSIDERATIONS

This is a randomised controlled trial therefore neither the parents/guardians nor the physicians will be able to choose the child's treatment.

A placebo has been included in the CAP-IT trial to make the treatments seem as similar as possible from the perspective of the parents/guardians and children. Furthermore, even closer similarity between the trial arms is achieved by preventing the investigators knowing which treatment the child is receiving (double-blind). Parents will therefore be unaware of which treatment group their child is in.

There will be one additional hospital visit for children in the trial although other additional contacts will be via telephone where possible. Travel costs for the additional visit will be available and a voucher will be given to participating families as compensation for their time.

11.2.2 ETHICAL APPROVALS

Before initiation of the trial at clinical sites, the protocol, all informed consent forms, and information materials to be given to the families will be submitted to an ethics committee for approval. Any further amendments will be submitted and approved by the ethics committee.

The rights of the families to refuse to participate in the trial without giving a reason must be respected. After the child has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the parent/guardian must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing the child's care.

11.3 COMPETENT AUTHORITY APPROVALS

This protocol will be reviewed by the MHRA and a REC.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. The CTA number for the trial is 00316/0246/001-0006.

The EudraCT number for the trial is 2016-000809-36.

The progress of the trial and safety issues will be reported to the competent authority, regulatory agency or equivalent in accordance with local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the MHRA and REC in a timely manner.

11.4 OTHER APPROVALS

The protocol will be approved by the HRA and the Sponsor will contact the NHS organisations to begin the process of site set up. Hospitals will be required to confirm that they have the capacity and capability to deliver the study. A copy of the PIS and Consent Form (CF) on local headed paper should be forwarded to the MRC CTU at UCL before participants are entered.

11.5 TRIAL CLOSURE

The trial will close when all participants have completed follow-up.

12 INDEMNITY

The Sponsor of the trial is University College London (UCL) and the trial is coordinated by the MRC CTU at UCL, part of the UCL Institute of Clinical Trials and Methodology.

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

13 FINANCE

CAP-IT is funded by the UK NIHR Health Technology Assessment (HTA) programme (project number 13/88/11) and by the MRC CTU at UCL.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in **figure 4**.

14.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MRC Clinical Trials Unit (CTU) at UCL. The TMG will be responsible for the day-to-day running and management of the trial. Full details of the TMG functioning, including the frequency of meeting and a list of TMG members can be found in the TMG Charter.

14.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair. The role of the TSC is to provide overall guidance for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

14.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The Independent Data Monitoring Committee (IDMC) will be the only group which sees the confidential, accumulating data for the trial separately by randomised group. Reports to the IDMC will be produced by the trial statisticians. The frequency of meetings will be dictated in the IDMC charter. The IDMC will consider data using the statistical analysis plan (see **Section 9.5**) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm be discontinued.

Further details of IDMC functioning, and the procedures for interim analysis and monitoring are provided in the IDMC Charter.

14.4 ENDPOINT REVIEW COMMITTEE (ERC)

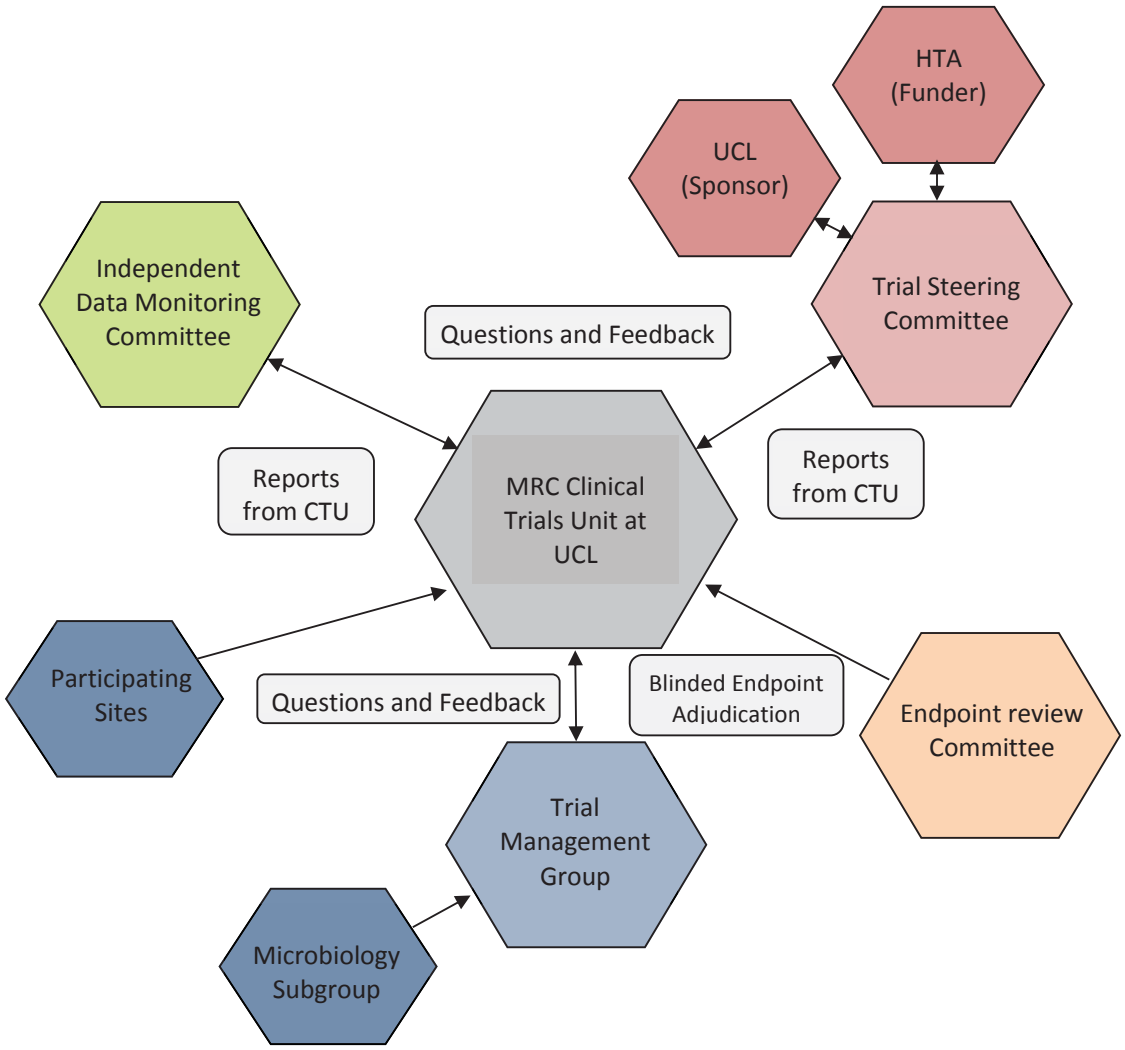
An Endpoint Review Committee (ERC), blinded to randomised allocations, will review all cases where the participant was prescribed non-trial antibacterial treatment. The main role of the Committee is to adjudicate, based on all available data, whether the primary outcome was met. The ERC will also provide advice to the CAP-IT Trial Management Team (TMT) and Trial Steering Committee (TSC) on any issues regarding trial endpoint ascertainment.

Further details of ERC functioning are provided in the ERC Charter.

14.5 ROLE OF STUDY SPONSOR

The sponsor of the trial is University College London, as employer of the staff coordinating the trial at MRC CTU.

Figure 4. Committees involved in study oversight



15 PUBLICATION

For the purposes of publication the results from the PED and WARD groups will be published together. The data from all centres will be analysed together and published as soon as possible in peer-reviewed journals, as well as being presented at national and/or international conferences. Individual groups and clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the TMG has published its report. The TMG will form the basis of the Writing Committee and will advise on the nature of all publications.

Data will not normally be released externally prior to the publication of the trial's main outcome measures. All requests for external data release will be approved by the TSC.

15.1 DISSEMINATION

The results of this trial will be submitted for Open Access publication in high impact peer-review journals likely to be read by health professionals in the management of CAP in children in the UK. The work will be presented at key medical conferences. To maximise the impact of the trial across Europe its findings will be disseminated more widely through abstracts for oral and poster presentations submitted to the main relevant national and international conferences.

Once the trial has been completed, all families who participated will be notified of the results by post or email. A study website will be developed providing information for collaborators, participants and the public, with the results of the trial eventually posted here. The social media presence of the organisations involved will also be used to highlight news about the trial.

For the main results of the trial a press release will be produced, in collaboration with the press office of the journal publishing the results, which will be distributed to the UK and European media, to encourage press coverage. This will enable a wider audience to be reached.

15.2 AUTHORSHIP AND ACKNOWLEDGEMENTS

There are expected to be a number of resulting publications and the authorship will vary for each. Individual authors are likely to include relevant members of the TMG and collaborators, as well as high-recruiting investigators. All participating centres and corresponding PIs will be acknowledged in all relevant publications by name and all relevant expert advisors and members of the TMG, TSC and IDMC will be listed. All families who participated in the trial will be thanked as a group (not by name).

16 PROTOCOL AMENDMENTS

This is version 3.4 of the protocol.

16.1 PROTOCOL

16.1.1 AMENDMENTS MADE TO PROTOCOL VERSION 1.0 13 APR 2016

1. Throughout – version and date updated to v2.0, 12-Aug-2016.
2. Throughout – addition of MREC reference number
3. Throughout – minor typographical corrections and amendments for consistency and clarity.
4. Page iii-iv – Trial contact details – addition of new contacts.
5. Page vii-viii & section 5 - Correction to the higher amoxicillin dose from 70-120mg/kg to 70-90mg/kg
6. Trial Assessment Schedule
    a. Inclusion of an additional phone call at day 4.
    b. Clarification regarding the physical exam at the final visit
    c. Change to duration of the symptom diary
7. Section 3 - clarifications and changes to the inclusion and exclusion criteria.
8. Section 6.1.2 – clarification on procedures for face to face visits
9. Section 6.2.1 – additional detail regarding the collection of nasopharyngeal swabs
10. Section 6.3.1 – additional detail regarding the collection of EDTA blood sample
11. Section 6.7.1 – additional information regarding storing parent/guardians email address and phone number and additional phone call at day 4.
12. Section 10.3 – addition of methodology sub-study.

16.1.2 AMENDMENTS MADE TO PROTOCOL VERSION 2.0 12 AUG 2016

MAJOR CHANGES	SECTION(S) AFFECTED
PED group **exclusion criteria 4** *"On systematic antibiotic treatment at presentation"* removed and additional **inclusion criteria 3** *"Prior antibiotic treatment: Not on systemic antibiotic treatment at presentation OR Treated in the community as an outpatient with uninterrupted oral or intravenous beta-lactam for ≤48 hours"* included to allow inclusion of children presenting with up to 48 hour's outpatient beta-lactam treatment.	▪ Summary of Trial ▪ 3 – Selection of Participants (3.1, 3.1.2, 3.1.3, 3.1.4)
Reference to the pilot occurring during the initial 6 months of the study change as this will now occur over 3 months during the first winter of recruitment.	▪ Summary of Trial ▪ 3 – Selection of Participants ▪ 9 – Statistical Considerations (9.6)
Inclusion criteria 1 for both PED and WARD groups edited from *"Age from 1 to 5 years (up to their 6th birthday)" to "greater than 6 months and weighing 6-24kg"* to facilitate inclusion of all children to whom the results of the trial may be relevant and whose treatment can be completed according to CAP-IT protocol using available IMP	▪ Summary of Trial ▪ 3 – Selection of Participants (3.1.2, 3.2.3)
Exclusion criteria 9 & 13 for PED and WARD groups, respectively, *"Weight <24kg"* deleted (explanation see above).	▪ 3 – Selection of Participants (3.1.3, 3.2.4)
The CAP diagnostic criteria relating to fever in **inclusion criteria 2** in both groups changed from *"Temperature ≥38^{o}C measured by any method OR history of fever in last 24 hours reported by parents/guardians"* to "*Temperature ≥38^{o}C measured by any method OR likely fever in last 48 hours"* to account for accompanying parent/guardian not necessarily having personally assessed temperature in the last 24 hours.	▪ 3 – Selection of Participants (3.1.2, 3.2.3)
The nasopharyngeal sample for WARD patients will be collected at randomisation to ensure availability of a baseline sample for comparison with the final sample. An optional additional sample may be taken prior to antibiotic treatment at admission.	▪ Trial Summary (Trial Schema, trial Assessment Schedule – WARD group) ▪ 3 – Selection of Participants (3.2.1, 3.2.5) ▪ 6 – Assessments & Follow-Up (6.2.1)
WARD inclusion criteria 6 edited from *"planned for discharge and to continue uninterrupted antibiotic treatment"* to *"Child is considered fit for discharge at randomisation".*	▪ 3 – Selection of Participants (3.2.3)
WARD exclusion criteria 9 *"current oxygen requirement"* deleted as is reflected in inclusion criteria 6.	▪ 3 – Selection of Participants (3.2.4)
WARD Exclusion criteria 10 *"current age specific tachypnoea"* deleted as is reflected in inclusion criteria 6.	▪ 3 – Selection of Participants (3.2.4)
Primary Outcome Measure updated to specify "*systemic antibacterial"* treatment to specify that topical antibacterials are not of interest.	▪ Summary of Trial ▪ 9 – Statistical Considerations (9.3.1)

OTHER CHANGES	SECTION(S) AFFECTED
Grammar and spelling corrections made and sections re-worded for clarity throughout	▪ Throughout
Version numbers and dates updated throughout	▪ Throughout
CTA number "17141803" added to front cover, summary and section 11.	▪ Summary of trial ▪ Front page
Contact details updated and Professor Diana Gibb included as a chief investigator alongside Professor Mike Sharland	▪ General Information ▪ Summary of Trial
In the summary, randomisation is clarified to be *"at discharge from hospital"*.	▪ Summary of Trial
Study Hypotheses 1 and 2 updated to include "*as determined by additional/ subsequent antibiotic treatment*" and "*in terms of resolution/ prevention of relapse of lower respiratory illness requiring re-treatment with antibiotics*" deleted from study hypothesis 1 to fall in line with details in body of protocol.	▪ Summary of Trial
PED Group trial assessment schedule updated to include blood sample sub-study. Additional explanatory notes updated as follows: ▪ Spelling correction of word physical ▪ Explanatory notes for saliva sampling and nasopharyngeal sampling separated and saliva sample wording changed to include *"if current saliva sampling kit can be used at site"* to account for sites unable to use saliva sample kits ▪ Explanatory note added for blood sample sub-study	▪ Summary of Trial (Trial Assessment Schedule – WARD GROUP)
WARD Group trial assessment schedule updated to allow for optional medical history, physical examination, symptom review, nasopharyngeal swab, saliva sample, haematology, biochemistry, virology, chest x-ray and stool sample to be taken pre-randomisation. Nasopharyngeal and saliva samples added to randomisation (d1). Additional explanatory notes also updated as follows: ▪ Explanatory notes for saliva sampling and nasopharyngeal sampling separated and saliva sample wording changed to include *"if current saliva sampling kit can be used at site"* to account for sites unable to use saliva sample kits ▪ For blood sample sub-study additional notes, *"in whom a blood culture is also taken"* deleted as blood can be taken from children having another routine blood test. ▪ For stool sample additional notes, *"within first 24 hours of hospitalisation"* deleted.	▪ Summary of Trial (Trial Assessment Schedule – WARD GROUP)

Background section re-ordered and partially re-worded in parts for clarity and reference to recent literature added. In addition, previously unavailable results from CAP-IT feasibility work (service evaluation) have been included. ▪ Changes to sections 1.1., 1.2. and 1.3. in response to feedback from TSC, mainly re-ordering of existing paragraphs for clarity. ▪ Relevant recent systematic review on optimal antibiotic treatment duration for a range of childhood infections and relevant studies recently registered on clinicaltrials.gov have been added to Section 1.4. ▪ Section 1.5 Rational for the trial has been expanded to include results from CAP-IT feasibility work, including an interpretation of these results in relation to the CAP-IT trial and proposed major modifications as outlined above.	▪ 1 – Background
Reference to site specific approval removed and replaced with local approval.	▪ 2 – Selection of Site/Clinicians (2.1)
Clarified that it is the investigator's responsibility to ensure that staff are available to recruit out-of-hours.	▪ 2 – Selection of Site/Clinicians (2.1.2)
"e.g.at least 50% or more of predicted recruitment" removed from pilot phase section as defined criteria agreed with the funder will be applied.	▪ 9 – Statistical Considerations (9.6)
Inclusion criteria 2 for both PED and WARD groups edited to clarify that clinical diagnosis of CAP is made at presentation.	▪ 3 – Selection of Participants (3.1.2, 3.2.3)
PED exclusion criteria 7 "I*nitial decision to treat with oral antibiotic other than amoxicillin on discharge from hospital"* deleted and an additional exclusion criterion added: *"Need for systemic treatment with an antibiotic other than amoxicillin on discharge from hospital."*	▪ 3 – Selection of Participants (3.1.3)
Current antibiotic treatment must be obtained at baseline, where applicable, for PED patients.	▪ 3 – Selection of Participants (3.1.4)
Nasopharyngeal sample in PED patients will be collected at randomisation following informed consent. No longer required to be prior to antibiotic treatment.	▪ 3 – Selection of Participants (3.1.4)
WARD inclusion criteria 5 edited to include *"on discharge from hospital"*	▪ 3 – Selection of Participants (3.2.3)
In the blood sample sub-study, *"if possible an additional EDTA blood sample should be collected before starting inpatient antibiotic treatment."*	▪ 3 – Selection of Participants (3.2.5)
Figure demonstrating treatment arms updated to replace DT (dispersible tablets) with mg/ml dosage.	▪ 5 – Treatment of Participants (5.2.3)
Instructions regarding type of scales to be used for children (baby scales for infants up to 24 months, sitting or standing scales for older children) deleted.	▪ 5 – Treatment of Participants (5.3)
Additional acceptable locations for storage of IMP added.	▪ 5 – Treatment of Participants (5.4)

Additional paragraph added *"In cases where there is an issue with tolerability of the trial medication resulting in recurrent spitting or gagging, this should be switched to an alternative amoxicillin formulation or another antibiotic if the child is still assessed to be in need of continued treatment. This mirrors routine clinical practice, and the decision to continue antibiotic treatment is based on the assessment of the child. No additional relevant information is likely to be identified from unblinding."*	▪ 5 – Treatment of Participants (5.6.1)
Website details added to unblinding information.	▪ 5 – Treatment of Participants (5.7)
Sentence *"regular medication will be recorded at enrolment"* deleted as there is no relevant regular medication that needs to be recorded for eligible children.	▪ 5 – Treatment of Participants (5.8.1)
"Common known side effects of amoxicillin" and *"Antibiotic treatment since last protocol contact, including, as appropriate, adherence to CAP-IT treatment and whether any additional/new antibiotic prescriptions were issued."* added to telephone contact and face-to-face visits (including acute events) sections.	▪ 6 – Assessments & Follow-Up (6.1.1, 6.1.2)
"If the final follow up is done by phone, the format of the visit will be the same as all other telephone follow up visits, as described in section 6.1.1." added to face-to-face visits (including acute events) section.	▪ 6 – Assessment & Follow-Up (6.1.2)
Saliva samples are only to be collected at sites in which the sample collection kits can be used.	▪ 6 – Assessment & Follow-Up (6.2.2) ▪ Summary of Trial (Trial Assessment Schedule)
PED patients to be included in the blood sample sub-study.	▪ 6 – Assessment & Follow-Up (6.3.1) ▪ Summary of Trial (Trial Assessment Schedule)
"This will be completed either in electronic or paper format and sites should follow instructions from MRC CTU regarding which format to use." Added to symptom diary section.	▪ 6 – Assessment & Follow-Up (6.7.1)
Lost to follow-up section re-worded and additional sentences added as follows: *"If an individual telephone follow-up visit is missed, the site team should continue to attempt to contact the parent via phone and/or email for all future visits, including the final face-to-face follow up"* and *"If the final follow up is done by phone, the format of the visit will be the same as all other telephone follow up visits, as described in section 6.1.1."*	▪ 6 – Assessment & Follow-Up (6.9)
"*Hospitalisations where no untoward or unintended response has occurred, e.g. social admissions"* removed as an exempted serious adverse event.	▪ 7 – Safety Reporting (7.1.3)
Only non-serious AEs or ARs that are listed in the clinical symptoms section of the study CRFs should be recorded on the CRF. All other AEs and ARs need only be recorded in the patient notes. Additional sentence added to section 7.2 *"All adverse events that lead to cessation of trial treatment should be recorded in the relevant section of the CRF".*	▪ 7 – Safety Reporting (7.2)
The severities of non-serious AEs and/or ARs do not need to be DAIDS graded.	▪ 7 – Safety Reporting (7.2.1.B)

Method of randomisation updated to include that randomisation is *stratified by clinical site*.	▪ 9 – Statistical Considerations (9.1)
"in terms of resolution/ prevention of relapse of lower respiratory illness" deleted from primary objective 1.	▪ 9 – Statistical Considerations (9.2)
Morbidity secondary outcome measure regarding adverse events updated from *"clinical adverse events, principally skin rashes and diarrhoea."* to "*Specified clinical adverse events, including thrush, skin rashes and diarrhoea."*	▪ 9 – Statistical Considerations (9.3.2A)
Microbiological secondary outcome measure updated from *"change in phenotypic resistance to penicillin in S. pneumoniae between randomisation (pre-randomisation in WARD) and week 4 measure as change in penicillin MIC in S. pneumoniae isolates colonising the nasopharynx."* to *"Phenotypic resistance to penicillin at week 4 measured in S. pneumoniae isolates colonising the nasopharynx."*	▪ 9 – Statistical Considerations (9.3.2B)
Sample Size changes Section re-ordered; Sentence about review of sample size assumptions re-worded for clarity	▪ 9 – Statistical Considerations (9.4)
Analysis Plan changes Section re-ordered; more details given for the analysis of the primary endpoint including sensitivity analyses.	▪ 9 – Statistical Considerations (9.7)

16.1.3 AMENDMENTS MADE TO PROTOCOL VERSION 3.0 1ST SEPTEMBER 2017

Key changes include:

- Statistical changes: Joint analysis of the PED & WARD groups, change to the primary endpoint definition, change to the non-inferiority margin (4-8%) and a consequent reduction in sample size from 2400 to 800 children.
- Addition of an Endpoint Review Committee (ERC).
- Addition of a procedure for collecting primary endpoint data from primary care for patients who are lost to follow-up or withdrawn.
- Modification of the WARD criteria to allow out-patient systemic antibacterial treatment prior to presentation as long as total treatment is <48 hours before randomisation.

Detailed changes:

1. Throughout – version and date updated.
2. Throughout – minor wording changes for clarification.
3. Throughout – reference to the saliva sample removed as no longer collected.
4. Throughout – reference to the blood sub-study removed as no longer planned.
5. Throughout – "inpatient" replaced with "in-hospital" in relation to prior beta-lactam treatment for WARD patients.
6. Address of sponsor updated page ii, iii & iv.
7. Summary of Trial – Study design, Type of Participants to be Studied and Setting sections updated to remove repeated wording. Wording of PED and WARD group definitions also updated, in particular to allow the inclusion of WARD patients with prior outpatient antibiotics.
8. Summary of Trial – Primary Outcome Measure section updated with new definition.
9. Summary of Trial – Minor wording changes to Secondary Outcome Measure section and health economic outcomes removed and added instead to ancillary studies section.
10. Summary of Trial – Randomisation section wording updated for clarity.
11. Summary of Trial – Number of participants to be studied section updated to 800 and wording included confirming that this is a minimum sample size and the TSC may choose to recruit beyond this.
12. Summary of Trial – Duration section updated to delete reference to pilot phase which has been completed.
13. Summary of Trial – Ancillary Studies/ Substudies section updated to include methodological sub-study and health-economics analyses as an ancillary study.
14. Trial schema – separate Ped and WARD trial schemas deleted and replaced with a joint schema without reference to saliva samples which are no longer collected.
15. Trial assessment schedule and explanatory notes – updated to reflect changes, including removal of saliva samples and blood sub-study.
16. Selection of Participants – PED and WARD group definitions updated for inclusion of WARD patients who have received outpatient antibiotics before admission as an inpatient
17. Selection of Participants – Minor changes to wording for clarification. Inclusion of "Lobar pneumonia on chest x-ray (if obtained) as part of the inclusion criteria 2 (both PED and WARD). WARD criteria updated for inclusion of patients with prior out-patient antibiotics before admission.
18. Selection of Participants – Figure updated to include WARD patients receiving community beta-lactam treatment before in-hospital treatment.
19. Treatment of Participants – Drug substitution section updated with guidance for handling IMP intolerance.
20. Treatment of Participants – figure updated with correct dose values.

21. Assessments and Follow Up – Procedures for assessing additional antibiotic treatment section updated to include procedure for sites contacting GPs of patients who have been lost to follow-up or withdrawn with consent for continued data collection.
22. Assessments and Follow Up – Additional wording to clarify that RNAlater samples should only be collected with additional optional written consent.
23. Statistical Considerations – Primary Outcome Measure, Sample Size and Analysis Plan sections updated following planned re-evaluation of statistical assumptions. Health economics analyses removed from secondary outcome section and added as an ancillary study pending additional funding.Figure 5 deleted.
24. Oversight and Trial Committees – Endpoint Review Committee (ERC) added and figure updated.

16.2 APPENDICES

16.2.1 AMENDMENTS MADE TO APPENDICES VERSION 1.0 13 APR 2016

1. Throughout – version and date updated to v2.0, 12-Aug-2016.
2. Throughout – addition of MREC reference number.
3. Appendix I – updated reference document.

16.2.2 AMENDMENTS MADE TO APPENDICES VERSION 2.0 12 AUG 2016

1. Throughout – document up versioned throughout.
2. Page 1 – CTA number added.
3. Appendix III – IDMC and TSC members added.

16.2.3 AMENDMENTS MADE TO APPENDICES VERSION 3.0 01 SEP 2017

1. Throughout – version and date updated
2. Throughout – CTA number updated to 00316/0246/001-0006.
3. Appendix I – "please record adverse events on the relevant CRF" deleted. Date of most recent update to reference document included.
4. Appendix III – Endpoint review committee added.

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Supplemental Online Content

Bielicki JA, Stöhr W, Barratt S, et al. Effect of amoxicillin dose and treatment duration on the need for antibiotic retreatment in children with community-acquired pneumonia: the CAP-IT randomized clinical trial. JAMA. doi: 10.1001/jama.2021.17843

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

eTable 1: Features defined as indicating presence of complicated pneumonia

CAP COMPLICATED BY SEPSIS	**CAP WITH SEVERE RESPIRATORY FAILURE**	**CAP WITH LOCAL COMPLICATIONS**
Presence of shock requiring >20ml/kg fluid resuscitation Hypotension as defined by Advanced Paediatric Life Support/European Paediatric Life Support guidelines	Altered mental state (Glasgow Coma Score<14 or AVPU scale <A) Requirement for invasive ventilation or non-invasive ventilatory support	Empyema Pleural effusion Pneumothorax Pulmonary abscess Other complications involving the pleural or pulmonary space
Paediatric intensive care unit admission (direct)		

eMethods 1: Full inclusion and exclusion criteria

CAP-IT recruited children via 2 different pathways:

1. PED group: children who are recruited in the Paediatric Emergency Department (PED) or Paediatric Assessment Unit (PAU). Children in this group will be treated at home with amoxicillin without receiving any in-hospital antibiotics. These children will be entered into the trial either prior to receiving any antibiotic prescription OR after ≤48 hours uninterrupted oral beta-lactam treatment in the community.
2. WARD group: children who are recruited from in-hospital paediatric hospital wards or paediatric assessment units (PAUs) following in-hospital treatment with beta-lactam antibiotics. Children in this group will receive ≤48 hours total treatment with any beta-lactam antibiotic prior to entering the trial. Treatment may start in the community before in-hospital treatment, provided treatment is uninterrupted.

PED Inclusion criteria

1. Age greater than 6 months and weighing 6 - 24kg
2. Clinical diagnosis of CAP at presentation to PED as defined by **all** of the following:
   - Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND
   - Temperature ≥38ºC measured by any method OR parent-reported fever within 48 hours prior to presentation AND
   - Signs of laboured/difficult breathing or focal chest signs at presentation in the PED (i.e. one or more of the following):
     a. Nasal flaring
     b. Chest retractions
     c. Abdominal breathing
     d. Focal dullness to percussion
     e. Focal reduced breath sounds
     f. Crackles with asymmetry
     g. Lobar pneumonia on chest X-ray (if obtained)
3. Prior antibiotic treatment:
   - Not on systemic antibiotic treatment at presentation OR
   - Treated in the community as an outpatient with uninterrupted oral beta-lactam antibiotics for ≤48 hours
4. Decision to treat with oral amoxicillin for CAP on discharge from hospital
5. Parent/guardian willing to accept all possible randomised allocations
6. Available for follow up for the entire study period, parent/guardian willing to be contacted by telephone at day 4, weeks 1, 2 and 3, and attend a face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Informed consent form for trial participation signed by parent/guardian.

PED Exclusion criteria

1. Severe underlying chronic disease with an increased risk of developing complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy

3. Any other known contra-indication to amoxicillin
4. Need for systemic treatment with an antibiotic other than amoxicillin on discharge from hospital
5. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia (see below)
7. Receipt of initial antibiotic treatment in hospital in PAU or on the ward
8. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

WARD Inclusion criteria

1. Age greater than 6 months and weighing 6 - 24kg.
2. Clinical diagnosis of CAP at presentation to hospital as defined by **all** of the following:
    - Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND;
    - Temperature ≥38ºC measured by any method OR likely fever within 48 hours prior to presentation AND;
    - Signs of laboured/difficult breathing or focal chest signs (i.e. one or more of the following):
        - Nasal flaring
        - Chest retractions
        - Abdominal breathing
        - Focal dullness to percussion
        - Focal reduced breath sounds
        - Crackles with asymmetry
        - Lobar pneumonia on chest X-ray (if obtained)
3. Prior antibiotic treatment including doses administered in hospital:
    - Treated in-hospital only with any oral or intravenous beta-lactam for ≤48 hours after admission
    - Treated initially in the community and subsequently in hospital with any oral or intravenous beta-lactam, without interruption, for ≤48 hours in total
4. Decision to further treat with oral amoxicillin for CAP on discharge from hospital
5. Child is considered fit for discharge at time of randomisation
6. Available for follow-up for the entire study period, parent/guardian willing to be contacted by telephone at weeks 1, 2 and 3 and attend face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Parent/guardian willing to accept all possible randomised allocations
8. Informed consent for trial participation signed by a parent/guardian.

WARD Exclusion criteria

1. Severe underlying chronic disease with an increased risk of complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
5. Complicated pneumonia (see below)
6. Receipt of antibiotic other than a beta-lactam during admission
7. If treated in the community prior to admission, receipt of a non-beta-lactam antibiotic in the community at presentation
8. Clinically relevant positive blood culture (i.e. positive blood culture and clinical decision to prolong intravenous treatment for more than 48 hours or inappropriate to switch to amoxicillin therapy)
9. Receipt of >48 hours oral or intravenous antibiotic treatment in total
10. Decision to treat with oral antibiotic other than amoxicillin on discharge from hospital
11. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

eTable 2: Weight bands for dosing of trial medication

WEIGHT BAND	WEIGHT RANGE	MLS PER DAY	MLS PER DOSE (BID)
1	<6.5kg	9	4.5
2	6.5-<8.5	12	6
3	8.5-<10.5	15	7.5
4	10.5-<13.5	19	9.5
5	13.5-<17kg	24	12
6	17-<21kg	30	15
7	21-24kg	33	16.5

Note: body weight in kg.

eMethods 2: Details of adherence assessment

Data on IMP adherence were elicited during follow-up calls and visits, including at unscheduled visits. At each time-point, parents/guardians were asked whether IMP had been stopped early, and if so the date of the last dose taken, and for which of the following reasons: CAP improved/cured, CAP worsened/not improving, gagging/spitting out/refusing. Additionally, parents/guardians were asked how many doses of each bottle were either missed or in which the full prescribed volume was not given.

eMethods 3: Details of microbiological analysis

At Children's Vaccine Centre (Bristol University) screening cultures for S. pneumoniae were performed by plating samples onto streptococcal selective agar COBA plates and incubation at 37°C and 5% CO2. Plates were examined at 24 and 48 hours and suspected alpha-haemolytic colonies confirmed by inhibition on optochin disc and solubility on bile salts. S. pneumoniae isolates received by the University of Antwerp underwent phenotypic penicillin-susceptibility testing by microbroth dilution across a dilution range for penicillin of 0.016 to 16 mg/L with interpretation according to EUCAST Clinical Breakpoint Tables v. 10.0. The breakpoints for S. pneumoniae for infections other than meningitis were used as follows:

a) Sensitive: minimal inhibitory concentration (MIC) ≤ 0.064 mg/L
b) Intermediate: considered penicillin non-susceptible, MIC 0.125 to 2 mg/L
c) Resistant: considered penicillin-resistant, MIC > 2 mg/L

The same approach was taken for amoxicillin susceptibility testing (isolates with MIC ≤ 0.5 mg/L = sensitive; MIC > 1 mg/L = resistant). S. pneumoniae ATCC49619 was used for quality control.

eMethods 4: Details of main protocol amendment

- Joint analysis of children presenting and immediately discharged from the emergency department (PED) and children discharged after an inpatient stay of <48 hours (WARD): Initially PED and WARD were treated as separate strata because of (1) an expected higher severity of CAP in the WARD group, (2) the expected differences in prior receipt of antibiotic for current episode impacting on the duration of treatment analysis, (3) the need for different trial procedures (consent process, enrolment, additional data capture during inpatient period for WARD group). However, based on the pilot phase the following key aspects emerged and formed the basis for the joint analysis of PED and WARD: (1) In a substantial proportion of participating hospitals, children were first seen in a Paediatric Assessment Unit (PAU), before either being formally admitted or discharged. This made the distinction between PED and WARD less relevant, especially as many PAUs admitted children for up to 48 hours. (2) Although clinical signs and symptoms at presentation to ED were (as expected) worse on average in WARD vs PED children, considerable overlap in the two distributions was observed. (3) Duration of prior antibiotic exposure in the WARD group was much shorter than anticipated: 54% less than 12 hours, 75% less than 24 hours. (4) There was no evidence of a difference between the primary endpoint rate between PED and WARD.
- Introduction of a blinded Endpoint Review Committee for adjudication of primary endpoints: Following the pilot phase with a much high primary endpoint rate than originally assumed, the primary endpoint was clarified to guard against the possibility of bias towards the null from a high rate of antibiotic re-prescribing during follow-up unrelated to the target outcome and trial randomisations. A blinded Endpoint Review Committee (ERC) was set up to adjudicate on reported primary endpoints to identify "ERC-adjudicated clinically indicated non-IMP antibiotic

prescribed for respiratory tract infection (including CAP)". The ERC included four independent clinician members (including the independent chair) and reviewed narrative summaries for all cases with non-trial systemic antibiotic prescriptions to identify the reason for prescribing (RTI or other). For RTI prescriptions, the ERC also assessed the likelihood that the retreatment was clinically indicated.

- Revision of the non-inferiority margin from 4% to 8%: Key assumptions in the original sample size calculation were (1) primary endpoint event rate of 5%, (2) non-inferiority (NI) margin of 4% based on 1-sided 95% CI, (3) power of 90% and (4) 15% loss to follow-up. The serious underestimation of the primary endpoint rate resulted in the original NI margin to be considered overly stringent with 8% clinically acceptable. Given the actual estimated primary endpoint rate from the pilot phase of 15%, the 8% NI margin was more conservative on a proportionate scale (8/15, 53%; 4/5, 80%) despite representing an increase.

eMethods 5: Stratification by PED and WARD groups in the CAP-IT trial

1. Background

The original CAP IT proposal and protocol were based on a fully stratified design according to whether children were recruited from the Paediatric Emergency Department (PED group) or from inpatient paediatric hospital wards (WARD group).

The key rationale for this was:

1. the WARD group would tend to include children with more severe community-acquired pneumonia (CAP).

2. children in the PED group would not have received any antibiotic prescription for the current episode, whereas most children in the WARD group would have received inpatient antibiotic treatment.

3. the need for different trial procedures for the two groups, including the consent process, enrolment, and additional data capture during the inpatient period for the WARD group.

Because of these major perceived differences we also proposed conducting separate analyses of the PED and WARD groups, and the sample size was calculated to enable adequate power within each group.

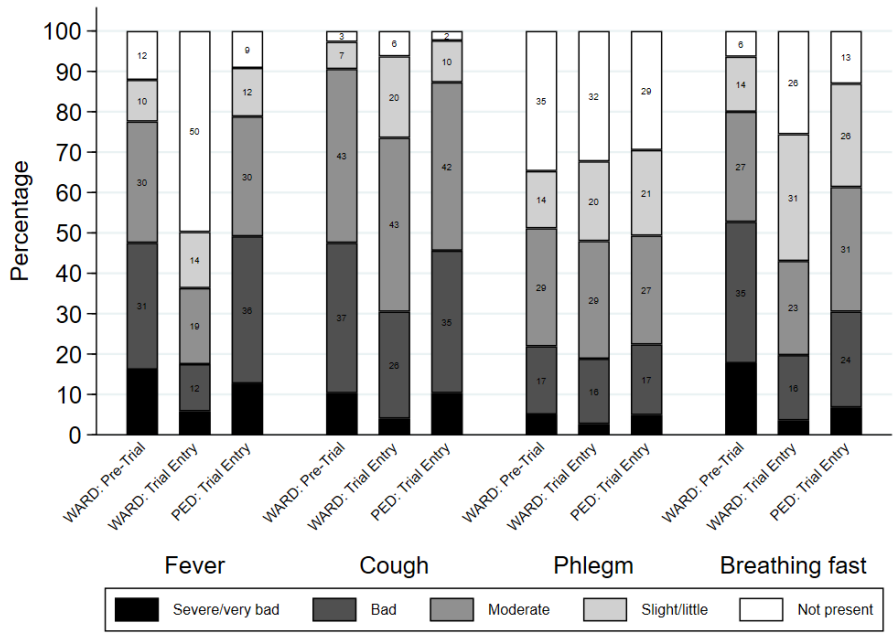
2. Data from the pilot phase

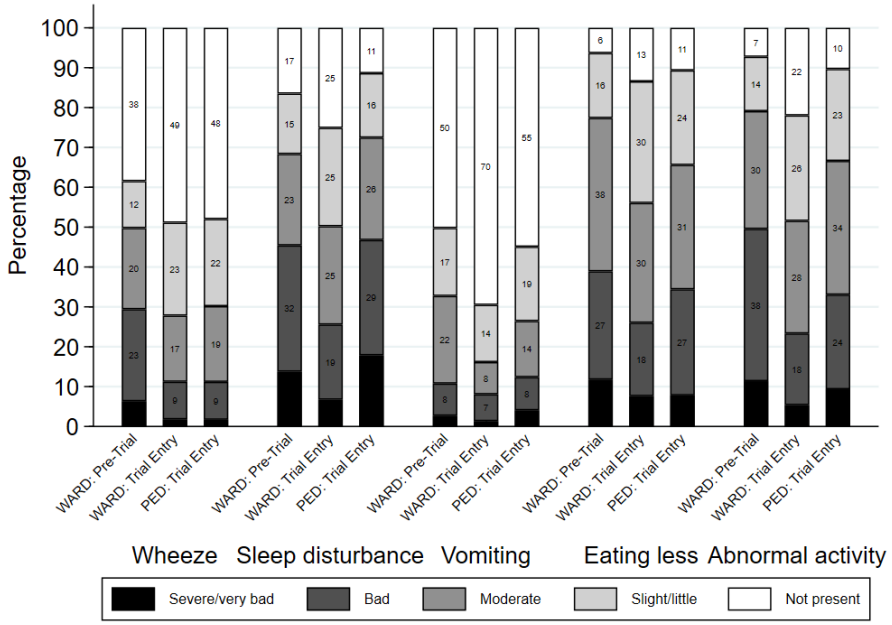
Emerging data from the trial suggested that there is no hard distinction between the PED and WARD groups.

1. In a substantial proportion of participating hospitals, children are first seen in a Paediatric Assessment Unit (PAU), before either being formally admitted or discharged. This makes the distinction between PED and WARD less relevant, especially as some PAUs admit children for up to 48 hours

2. Although clinical signs and symptoms at presentation to ED were slightly worse on average in WARD than in PED children, there was nevertheless considerable overlap in the two distributions (Figure 1). Also, there was rapid improvement in many WARD children between presentation and enrolment, to the extent that the direction of this difference was reversed.

Figure: Parent-reported symptoms at presentation and at enrolment in original PED and WARD groups





3. The protocol allows for up to 48 hours treatment with a beta-lactam. However, the duration of prior exposure in the WARD group is generally much shorter than this: 55% less than 12 hours, 75% less than 24 hours. Therefore, the impact of pre-treatment on the interpretation of the trial will be less critical.

3. Changes to the protocol: Joint analysis of PED and WARD groups
These issues were extensively discussed at the joint TSC/IDMC meeting in June 2017 and at the separate IDMC and TSC meetings in January 2018. There was consensus and strong support for simplifying the protocol by removing the distinction between the PED and WARD groups (although the difference will remain for some practical aspects of the trial, including how the trial drug is accessed). This change would make the study more generalisable to the broad question of duration and dose of antibiotics for children with CAP. By specifying that out of hospital or inpatient pre-treatment with beta-lactam antibiotics had to be a maximum of 48 hours, very severe cases of CAP requiring prolonged inpatient management and antibiotic treatment were excluded from the trial. The TSC and IDMC also considered that it would be more logical to conduct a single, overall analysis that controls for prior antibiotic exposure rather than the location of enrolment. Furthermore, the TSC and IDMC stressed that the most clinically relevant question of duration and dose of therapy to be given at home would be considered for all children at the point of discharge. This practically resulted a reduced overall sample size since information from all participants was to be considered together in assessing whether the non-inferiority criterion has been met.

4. Further detail for handling of PED and WARD pathways in main trial
The PED and WARD stratification was maintained for practical reasons to facilitate access to trial medication for children managed in different care settings within participating hospitals. Hence, after the amendment children were recruited through two different pathways. Children in either pathway may have had up to 48 hours of oral or parenteral beta-lactam treatment before enrolment.

eMethods 6: Rationale for change in the non-inferiority margin

1. Background
Key assumptions in the original sample size calculation for CAP-IT were:

1. primary endpoint event rate of 5% based on non-UK data.

2. non-inferiority margin of 4%.

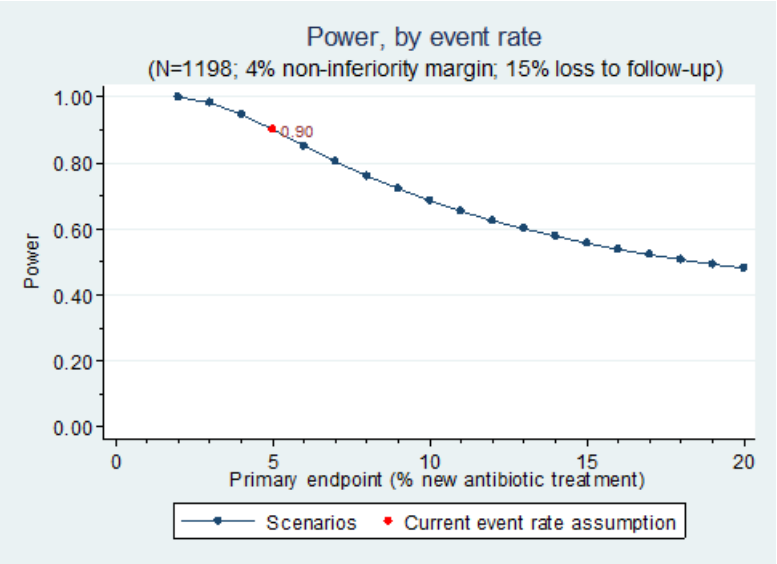
3. expected loss to follow-up of 15%.

The first assumption was highly uncertain due to the paucity of previous trials and observational studies with a similar endpoint in a similar setting. The protocol states: “There is uncertainty in this assumption (as with all trials in a new area), and a key role of the IDMC will be to review the accuracy of this assumption from accumulating data.” Accordingly, the IDMC reviewed unblinded data at their meeting on 15 January 2018.

2. Data from the pilot phase

The estimate of all-cause antibiotic retreatment in the report to the IDMC was 20.3% (95% CI 15.0-27.1) by Kaplan-Meier analysis (i.e. accounting for incomplete follow-up). A considerable proportion of these antibiotic retreatments would be expected to be clinically indicated and for respiratory tract infections. The initial assumption about the primary endpoint event rate was therefore a serious underestimate. The figure below shows how the power decreases as the event rate increases, if the non-inferiority margin remains fixed at 4% (absolute difference). This may seem paradoxical as intuitively there is more information in a trial with a larger number of events. The paradox arises as the risk difference is estimated less precisely the higher the overall event rate.

Figure: Change of statistical power over a range of different event rates



3. Changes to the protocol: Adjustment of the non-inferiority margin to 8%
In their report to the TSC, the IDMC recommended:

"We had an extensive discussion on a document prepared by the Trial Statisticians on a re-examination of the sample size calculation. This was prompted by a much high primary endpoint event rate than originally anticipated. We favour retaining the risk difference as the primary effect measure (rather than switching to an odds ratio) but using a more generous non-inferiority margin."

The rationale for a more generous non-inferiority margin was the need to consider this parameter in the context of the underlying event rate, and to avoid the paradox described in the previous section. The IDMC did not stipulate a new non-inferiority margin, instead this was discussed with the TSC. Various options were discussed, and a consensus was reached to change the margin to 8%, considering both statistical and pragmatic factors. Although this is double the original non-inferiority margin, it is more conservative on a proportionate scale (8/20, 40%; 4/5, 80%).

At the time it was acknowledged that the selection of an 8% non-inferiority margin was arbitrary but conservative considering guidance available at the time for antibiotic trials using similar clinical endpoints. Guidelines from the Infectious Diseases Society of America propose a non-inferiority margin of between 5 and 10% for trials in CAP with mortality endpoints but indicated that margins up to 20% are appropriate for clinical response endpoints.

Considering a rate of the primary outcome to be approximately 15%, an 8% non-inferiority margin assessed against an upper 1-sided 95% CI, and 15% loss to follow-up, 800 children needed to be randomised to achieve 90% power. This was regarded as a minimum sample size. As before, the calculation assumed no interaction between the two factorial randomisations. It was noted that a trial of 800 children was expected to generate 120 endpoints: If these were approximately equally split between two groups being compared, this would constitute strong clinical evidence of non-inferiority while also giving considerable latitude for sensitivity and sub-group analyses.

eMethods 7: Pre-specified sensitivity and subgroup analyses

The primary analysis of the primary endpoint included only those endpoints accepted by the ERC. The following sensitivity analyses for the primary endpoint were pre-defined in the Statistical Analysis Plan:

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.

In addition, the following subgroup analysis was also defined:

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.

eMethods 8: Post-hoc on-treatment analysis

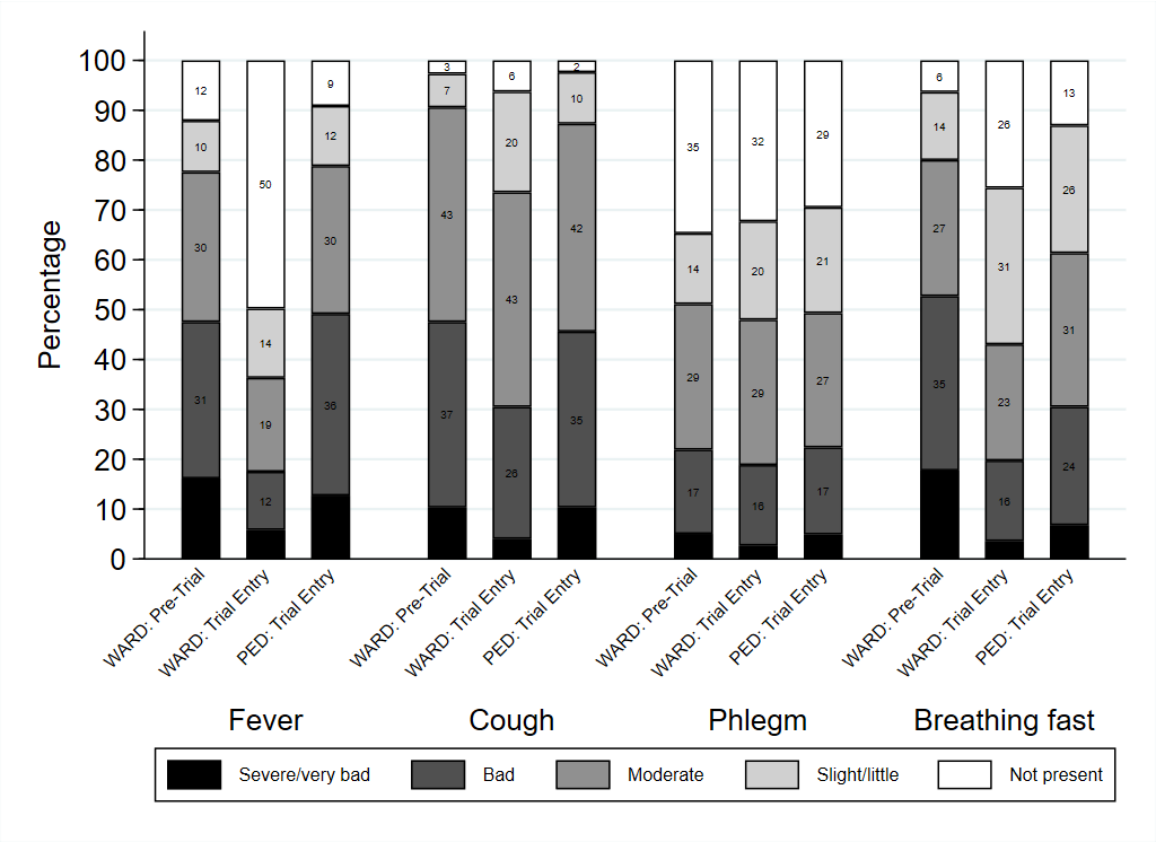
Overall non-adherence to trial medication, for the purposes of the on-treatment analysis of the primary endpoint, is defined as having taken less than 80% of trial medication as scheduled (i.e. more than 2 doses not taken or taken at smaller volume). However, switch from trial medication to non-trial antibiotics due to deterioration will not be regarded as non-adherence. The on-treatment analysis will exclude participants who were non-adherent to trial medication using two approaches: 1) non-adherence based on all trial medication including placebo, and 2) non-adherence based on active drug only.

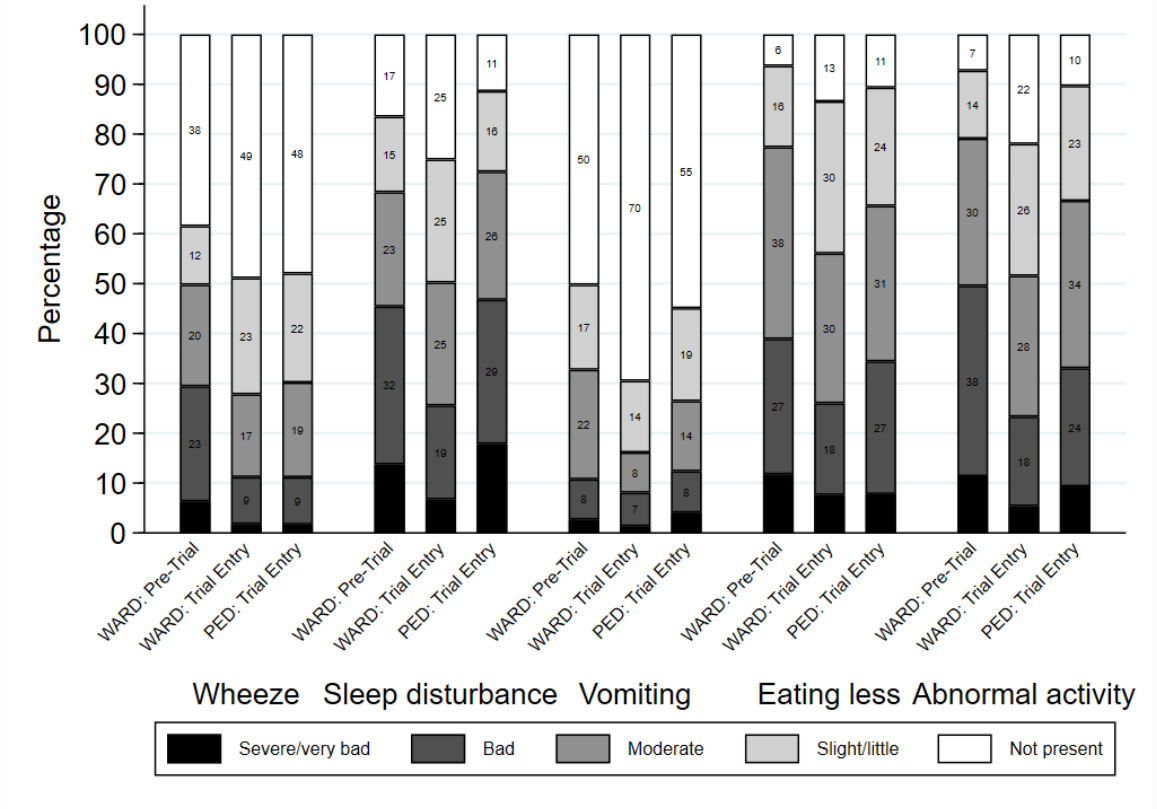
eMethods9: Post-hoc subgroup analysis by PED and WARD pathways

The PED pathway contained children who had not received any in-hospital antibiotic treatment (but may have had up to 48 hours of beta-lactam antibiotics in the community), while the WARD pathway contained children who received any in-hospital oral or IV beta-lactam therapy prior to randomisation. Children in the latter group may have received beta-lactam treatment in the community first and in hospital subsequently, without interruption, for a total of less than 48 hours. This subgroup analysis will evaluate the primary endpoint rate within each subgroup for each of the two randomizations.

eResults

eFigures 1 a and b: CAP symptoms at pre-trial entry in WARD, and at trial entry in PED and WARD





eTable 3: Participant characteristics at presentation, by dose and duration randomisations

		Total (n=814)	**Lower** (n=410)	**Higher** (n=404)	**Shorter** (n=413)	**Longer** (n=401)
Characteristics	Age (y)	2.5 (1.6,3.7)	2.5 (1.6, 3.7)	2.4 (1.6, 3.7)	2.5 (1.7, 3.7)	2.5 (1.5, 3.7)
	Male sex	421 (52%)	210 (51%)	211 (52%)	217 (53%)	204 (51%)
	Ethnicity					
	White	554 (68%)	275 (67%)	279 (69%)	283 (69%)	271 (68%)
	Asian or British Asian	106 (13%)	55 (13%)	51 (13%)	53 (13%)	53 (13%)
	Black or Black British	76 (9%)	40 (10%)	36 (9%)	40 (10%)	36 (9%)
	Mixed/other	78 (10%)	40 (10%)	38 (9%)	37 (9%)	41 (10%)
Medical history	Asthma or inhaler use within past month	255 (31%)	119 (29%)	136 (34%)	125 (30%)	130 (32%)
	Allergy or eczema	229 (28%)	115 (28%)	114 (28%)	108 (26%)	121 (30%)
	Prematurity	86 (11%)	43 (10%)	43 (11%)	51 (12%)	35 (9%)
	Other underlying disease	56 (7%)	37 (9%)	19 (5%)	21 (5%)	35 (9%)
	Routine vaccinations					
	Yes	773 (95%)	388 (95%)	385 (95%)	394 (95%)	379 (95%)
	No	26 (3%)	14 (3%)	12 (3%)	15 (4%)	11 (3%)
	Unknown	15 (2%)	8 (2%)	7 (2%)	4 (1%)	11 (3%)
History of current complaint	Duration of cough (d)	4 (2, 7)	4 (2, 6)	4 (2, 7)	4 (2, 7)	4 (2, 6)
	Duration of fever (d)	3 (1, 4)	3 (2, 4)	3 (1, 4)	3 (2, 4)	2 (1, 4)
	Systemic antibiotics in last 3 months	129 (16%)	64 (16%)	65 (16%)	66 (16%)	63 (16%)
	Systemic antibiotics in last 48 hrs	242 (30%)	119 (29%)	123 (30%)	123 (30%)	119 (30%)
	<12 hrs	100 (12%)	50 (12%)	50 (12%)	53 (13%)	47 (12%)
	12 - <24 hrs	85 (10%)	39 (10%)	46 (11%)	43 (10%)	42 (10%)
	≥24 hrs	57 (7%)	30 (7%)	27 (7%)	27 (7%)	30 (7%)
Clinical examination	Weight (kg)	13.5 (11.2,16.4)	13.6 (11.2,16.8)	13.3 (11.1,16.2)	13.8 (11.5,16.4)	13.2 (10.9,16.4)
	Temperature (°C)	38.1 (37.2, 38.8)	38.1 (37.3, 38.9)	38.0 (37.2, 38.6)	38.0 (37.1, 38.7)	38.1 (37.3, 38.8)
	Abnormal temperature	441 (54%)	227 (55%)	214 (53%)	221 (54%)	220 (55%)
	Heart rate (beats/min)	145 (130,160)	146 (131,160)	143 (130,158)	144 (131,158)	146 (130,162)
	Abnormal heart rate	578 (71%)	307 (75%)	271 (67%)	282 (68%)	296 (74%)
	Respiratory rate (breaths/min)	37 (30,44)	37 (30, 44)	38 (32, 44)	36 (30, 43)	38 (32, 45)
	Abnormal respiratory rate	528 (65%)	270 (66%)	258 (64%)	262 (64%)	266 (67%)
	Oxygen saturation (%)	96 (95,98)	96 (95, 98)	96 (95, 98)	96 (95, 98)	96 (95, 98)
	Abnormal oxygen saturation	43 (5%)	18 (4%)	25 (6%)	18 (4%)	25 (6%)
	Nasal flaring	75 (9%)	33 (8%)	42 (10%)	35 (9%)	40 (10%)
	Chest retractions	483 (59%)	239 (58%)	244 (60%)	239 (58%)	244 (61%)
	Pallor	169 (21%)	82 (20%)	87 (22%)	93 (23%)	76 (19%)
	Dullness to percussion Absent	380 (86%)	194 (86%)	186 (86%)	198 (86%)	182 (86%)
	Unilateral	59 (13%)	32 (14%)	27 (13%)	31 (13%)	28 (13%)
	Bilateral	3 (1%)	0 (0%)	3 (1%)	1 (<1%)	2 (1%)
	Bronchial breathing Absent	546 (82%)	283 (82%)	263 (82%)	276 (83%)	270 (81%)
	Unilateral	103 (15%)	53 (15%)	50 (16%)	49 (15%)	54 (16%)
	Bilateral	17 (3%)	10 (3%)	7 (2%)	8 (2%)	9 (3%)
	Reduced breath sounds Absent	389 (50%)	202 (52%)	187 (49%)	202 (51%)	187 (50%)
	Unilateral	336 (44%)	168 (43%)	168 (44%)	174 (44%)	162 (43%)
	Bilateral	46 (6%)	20 (5%)	26 (7%)	20 (5%)	26 (7%)
	Crackles crepitations Absent	134 (17%)	69 (17%)	65 (17%)	71 (18%)	63 (16%)
	Unilateral	562 (71%)	287 (71%)	275 (70%)	290 (72%)	272 (69%)
	Bilateral	100 (13%)	48 (12%)	52 (13%)	42 (10%)	58 (15%)

Note: Results are number (%) or median (IQR). Abnormal parameters: Temperature ≥ 38°C; Respiratory rate: >37/min for age 1-2 years; >28/min for age ≥3 years; Heart rate: >140/min for age 1-2 years; >120/min for age ≥3 years; Oxygen saturation: <92%.

eTable 4: Chest x-ray results at trial entry as reported by sites

	Lower	Higher	Shorter	Longer
	N=192	N=199	N=196	N=195
Result of chest x-ray				
Suggestive of pneumonia: lobar infiltrate	65 (33.9%)	69 (34.7%)	64 (32.7%)	70 (35.9%)
Suggestive of pneumonia: patchy infiltrate	72 (37.5%)	82 (41.2%)	84 (42.9%)	70 (35.9%)
Unsure if suggestive of pneumonia	21 (10.9%)	16 (8.0%)	15 (7.7%)	22 (11.3%)
Other diagnosis	7 (3.6%)	5 (2.5%)	6 (3.1%)	6 (3.1%)
No finding/not suggestive of pneumonia	27 (14.1%)	27 (13.6%)	27 (13.8%)	27 (13.8%)

eTable 5: Inpatient management for children in the WARD group

	Lower	Higher	Shorter	Longer	Total
	N=107	N=116	N=114	N=109	N=223
Any supportive measures?	56 (52%)	65 (56%)	59 (52%)	62 (57%)	121 (54%)
-Oxygen?	50 (47%)	60 (52%)	54 (47%)	56 (51%)	110 (49%)
-Nasogastric feeds or fluids?	4 (4%)	2 (2%)	2 (2%)	4 (4%)	6 (3%)
-Parenteral fluids?	5 (5%)	14 (12%)	9 (8%)	10 (9%)	19 (9%)
-Chest physiotherapy?	3 (3%)	3 (3%)	3 (3%)	3 (3%)	6 (3%)
-Other supportive measures?	0	0	0	0	0
Any non-antibiotic treatments given?	86 (80%)	97 (84%)	91 (80%)	92 (84%)	183 (82%)
-Salbutamol inhaled?	57 (53%)	73 (63%)	60 (53%)	70 (64%)	130 (58%)
-Steroids?	24 (22%)	27 (23%)	25 (22%)	26 (24%)	51 (23%)
-Salbutamol IV?	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
-Other non-antibiotic treatments	54 (50%)	67 (58%)	59 (52%)	62 (57%)	121 (54%)

eTable 6: Prior exposure to antibiotics

	Lower	Higher	Shorter	Longer	Total
	N=410	N=404	N=413	N=401	N=814
Antibiotics received in last 48 hours?					
Yes	119 (29%)	123 (30%)	123 (30%)	119 (30%)	242 (30%)
No	291 (71%)	281 (70%)	290 (70%)	282 (70%)	572 (70%)
Class of prior antibiotic					
β-lactam	118 (99%)	123 (100%)	123 (100%)	118 (99%)	241 (100%)
Macrolide	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Name of prior antibiotic					
Amoxicillin	103 (87%)	106 (86%)	104 (85%)	105 (88%)	209 (86%)
Benzylpenicillin	1 (1%)	2 (2%)	1 (1%)	2 (2%)	3 (1%)
Ceftriaxone	2 (2%)	4 (3%)	3 (2%)	3 (3%)	6 (2%)
Cefuroxime	2 (2%)	0 (0%)	2 (2%)	0 (0%)	2 (1%)
Clarithromycin	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Co-amoxiclav	9 (8%)	11 (9%)	13 (11%)	7 (6%)	20 (8%)
Phenoxymethylpenicillin	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Number of prior antibiotic doses	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Time since first antibiotic					
<12 hrs	50 (42%)	50 (41%)	53 (43%)	47 (39%)	100 (41%)
12 - <24 hrs	39 (33%)	46 (37%)	43 (35%)	42 (35%)	85 (35%)
24 - <36 hrs	12 (10%)	16 (13%)	14 (11%)	14 (12%)	28 (12%)
>=36 hrs	18 (15%)	11 (9%)	13 (11%)	16 (13%)	29 (12%)
Time since first antibiotic	13.6 (5.0, 24.6)	13.9 (5.7, 23.0)	13.0 (5.0, 22.7)	14.0 (6.6, 24.6)	13.9 (5.6, 23.6)
Prior antibiotic: route					
Intravenous	15 (13%)	10 (8%)	17 (14%)	8 (7%)	25 (10%)
Oral	103 (87%)	110 (89%)	106 (86%)	107 (90%)	213 (88%)
Intravenous + oral	1 (1%)	3 (2%)	0 (0%)	4 (3%)	4 (2%)
Duration of prior antibiotic treatment					
<12 hrs	67 (56%)	66 (54%)	68 (55%)	65 (55%)	133 (55%)
12 - <24 hrs	27 (23%)	33 (27%)	33 (27%)	27 (23%)	60 (25%)
24 - <36 hrs	13 (11%)	17 (14%)	13 (11%)	17 (14%)	30 (12%)
36 - <=48 hrs	12 (10%)	7 (6%)	9 (7%)	10 (8%)	19 (8%)

eTable 7: Summary of ERC review

	Lower	Higher	Shorter	Longer
	N=410	N=404	N=413	N=401
Number of re-treatment events reviewed	76	67	77	66
By participant:				
Any retreatment reviewed by the ERC				
yes	74 (18.0%)	65 (16.1%)	73 (17.7%)	66 (16.5%)
no	336 (82.0%)	339 (83.9%)	340 (82.3%)	335 (83.5%)
# of ERC events per participant				
1	72 (97%)	63 (97%)	69 (95%)	66 (100%)
2	2 (3%)	2 (3%)	4 (5%)	0 (0%)

eTable 8: Reasons for starting non-trial systemic antibacterials, as adjudicated by the ERC

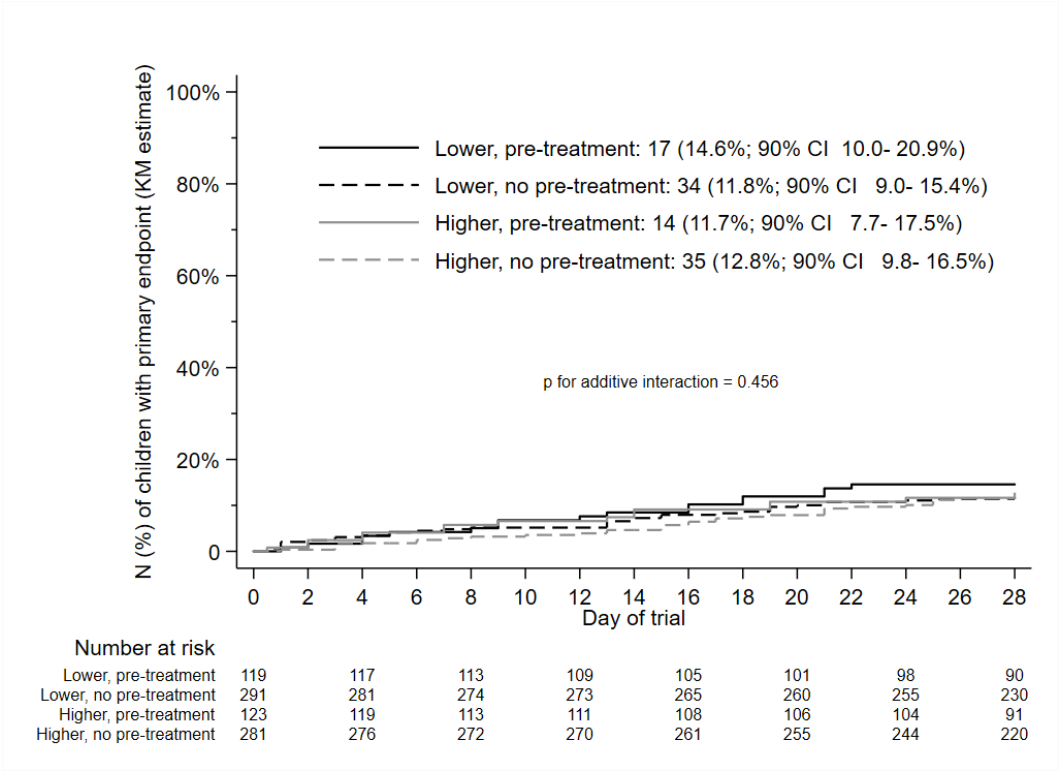
	Lower	Higher	Shorter	Longer
	N=74	N=65	N=73	N=66
CAP / Chest Infection	38	40	40	38
Other respiratory tract infection	19	12	18	13
Otitis Media	7	3	6	4
URTI	7	2	4	5
Tonsillitis	3	5	5	3
Other [a]	2	2	3	1
Other bacterial infection	8	7	9	6
Skin Infection	2	2	3	1
Urinary Tract Infection	2	2	3	1
Cellulitis	1	2	2	1
Scarlet Fever	1	1	0	2
Nail Infection	1	0	0	1
Salmonella Gastroenteritis	1	0	1	0
Other illness / injury	4	2	3	3
Appendicitis	1	0	1	0
Asthma	0	1	0	1
Bronchospasm/ Asthma	1	0	1	0
Dental Abscess	0	1	1	0
Lymphadenitis	1	0	0	1
Prophylaxis	1	0	0	1
Intolerance to IMP/adverse event	3	5	5	3
Vomiting	1	4	4	1
Diarrhoea	1	0	0	1
Rash	0	1	0	1
Refusing IMP	1	0	1	0
Parental preference	3	0	0	3
Pharmacy/admin error	1	1	2	0

eTable 9: Description of the primary endpoint

Patients who started systemic non trial antibacterials	Lower	Higher	Shorter	Longer
	N=51	N=49	N=51	N=49
Primary reason for starting new antibacterials				
CAP / Chest Infection	37 (73%)	39 (80%)	39 (76%)	37 (76%)
Otitis Media	5 (10%)	3 (6%)	4 (8%)	4 (8%)
Tonsillitis	3 (6%)	5 (10%)	5 (10%)	3 (6%)
URTI	5 (10%)	2 (4%)	3 (6%)	4 (8%)
Other respiratory tract infection	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Clinical indication				
Definitely/Probably	19 (37%)	19 (39%)	19 (37%)	19 (39%)
Possibly	32 (63%)	30 (61%)	32 (63%)	30 (61%)
First new antibiotic				
Amoxicillin	25 (49%)	24 (49%)	23 (45%)	26 (53%)
Amoxicillin, iv	0 (0%)	1 (2%)	1 (2%)	0 (0%)
Azithromycin	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Azithromycin+Amoxicillin, iv	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Cefuroxime	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Cefuroxime+Clarithromycin	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Clarithromycin	8 (16%)	9 (18%)	13 (25%)	4 (8%)
Co-amoxiclav	5 (10%)	5 (10%)	2 (4%)	8 (16%)
Co-amoxiclav+Azithromycin	2 (4%)	0 (0%)	0 (0%)	2 (4%)
Co-amoxiclav, iv	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Erythromycin	3 (6%)	4 (8%)	3 (6%)	4 (8%)
Phenoxymethylpenicillin	2 (4%)	4 (8%)	4 (8%)	2 (4%)
Who prescribed?				
CAP-IT Investigator	3 (6%)	3 (7%)	3 (6%)	3 (7%)
Other hospital doctor	18 (38%)	16 (36%)	17 (36%)	17 (37%)
GP	24 (50%)	25 (56%)	27 (57%)	22 (48%)
Other	3 (6%)	1 (2%)	0 (0%)	4 (9%)
Time new antibiotic started				
Day 1 to 15	29 (57%)	25 (51%)	28 (55%)	26 (53%)
Day 16 to 29	22 (43%)	24 (49%)	23 (45%)	23 (47%)

eFigures 2 a and b: Primary endpoint, analysis of interactions

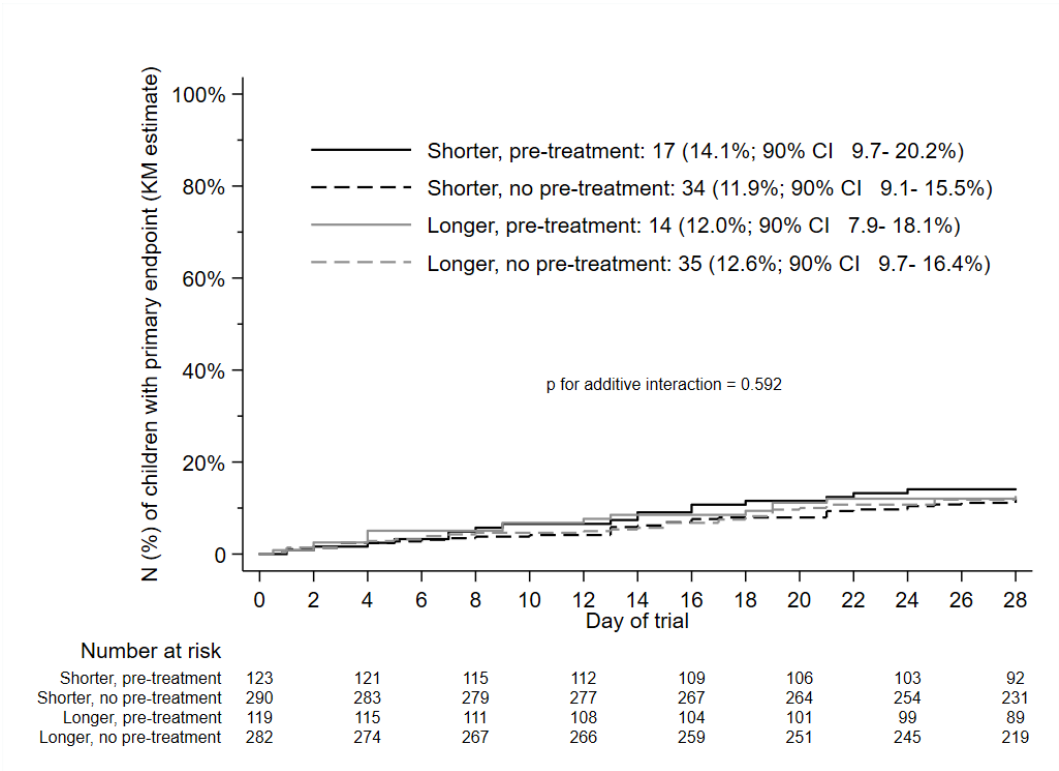
a) Interaction between pre-treatment with antibiotics and dose randomisation



Number at risk

Lower, pre-treatment	119	117	113	109	105	101	98	90
Lower, no pre-treatment	291	281	274	273	265	260	255	230
Higher, pre-treatment	123	119	113	111	108	106	104	91
Higher, no pre-treatment	281	276	272	270	261	255	244	220

b) Interaction between pre-treatment with antibiotics and duration randomisation

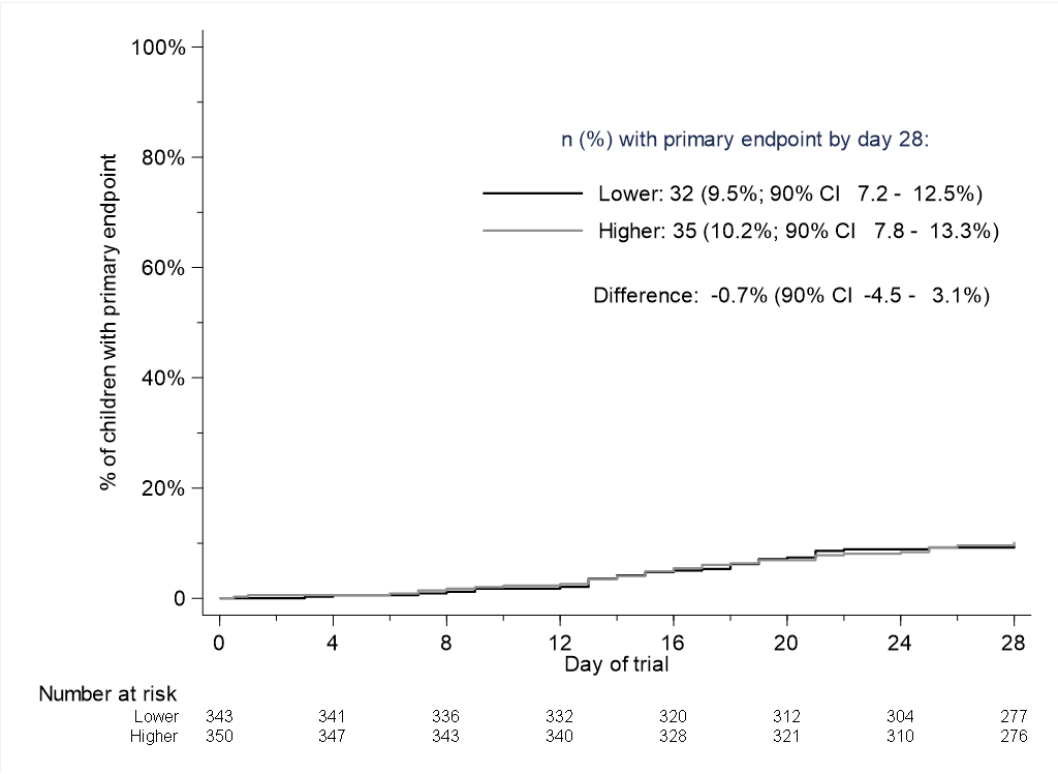


Number at risk

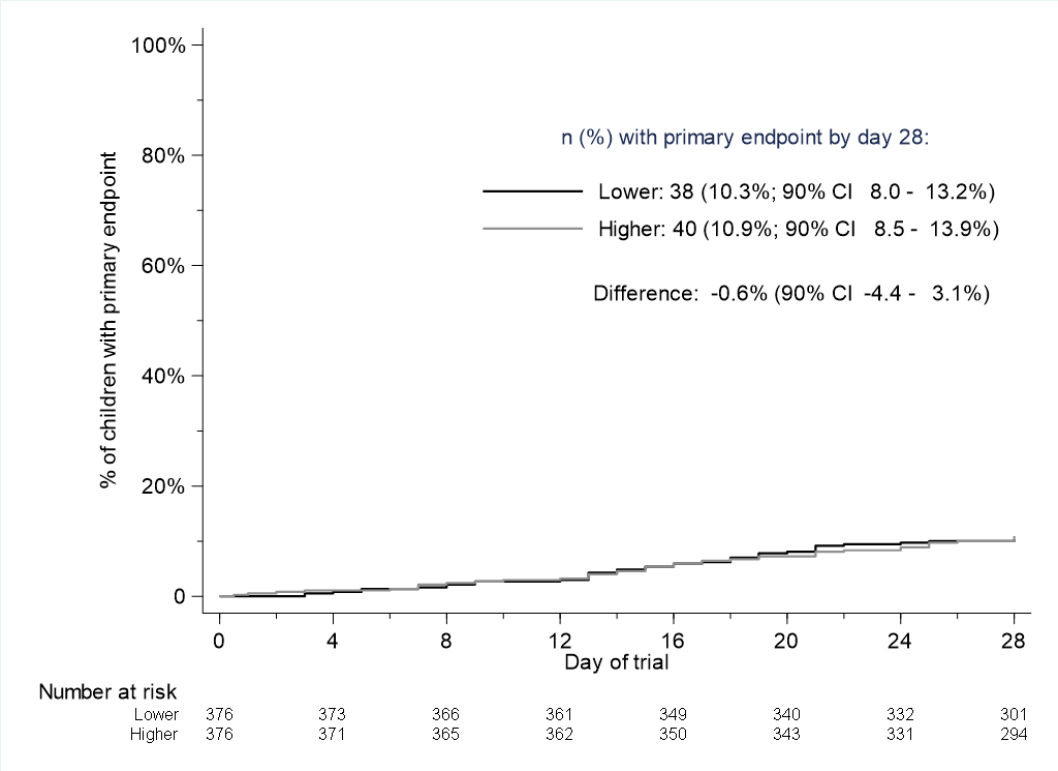
Shorter, pre-treatment	123	121	115	112	109	106	103	92
Shorter, no pre-treatment	290	283	279	277	267	264	254	231
Longer, pre-treatment	119	115	111	108	104	101	99	89
Longer, no pre-treatment	282	274	267	266	259	251	245	219

eFigures 3 a and b: On-treatment analysis of dose randomisation

a) Non-adherence based on all trial medication including placebo

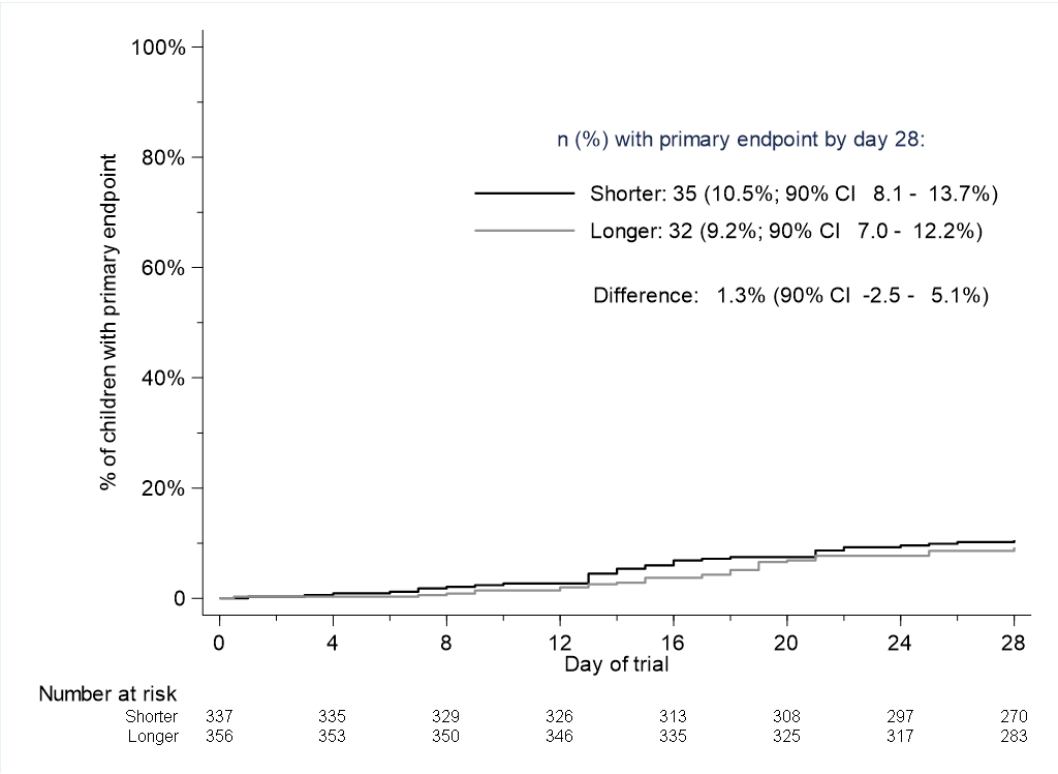


b) Non-adherence based on active trial drug only

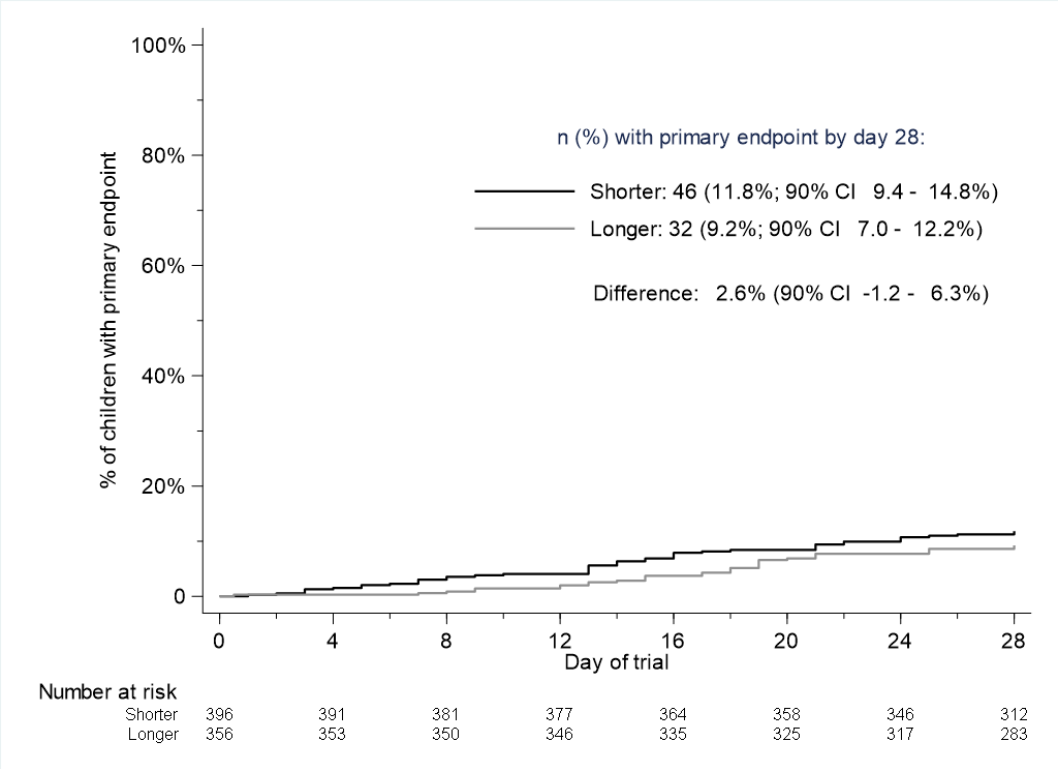


eFigures 4 a and b: On-treatment analysis of duration randomisation

a) Non-adherence based on all trial medication including placebo

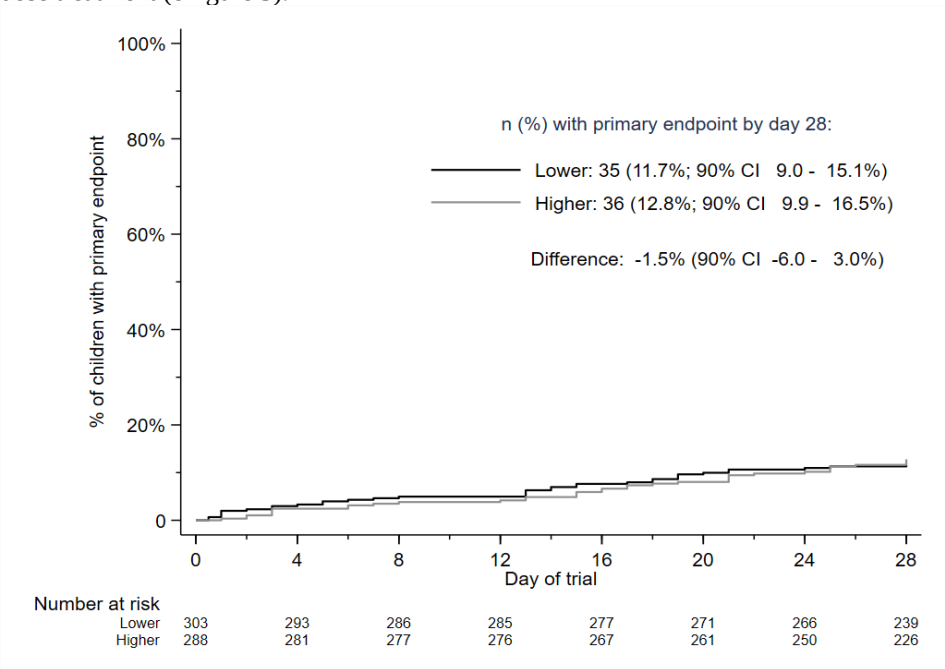


b) Non-adherence based on active trial drug only



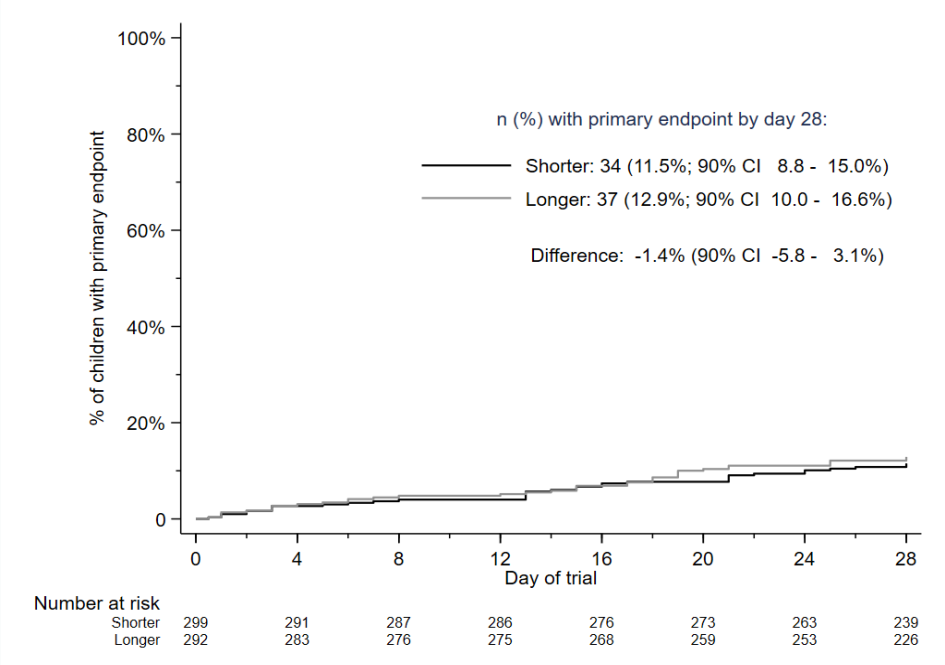
eFigure 5: Primary endpoint analysis for dose randomisation in PED pathway

Among 591 children in the PED pathway, primary endpoints occurred in 71 (12.2%) of children. Primary endpoint rates were 35/303 (11.7%) versus 36/288 (12.8%) in the lower dose and higher dose amoxicillin treatment groups (difference -1.5% (90%CI -6.0 to 3.0%)). For children in the PED pathway, lower dose treatment was therefore noninferior to higher dose treatment (eFigure 5).



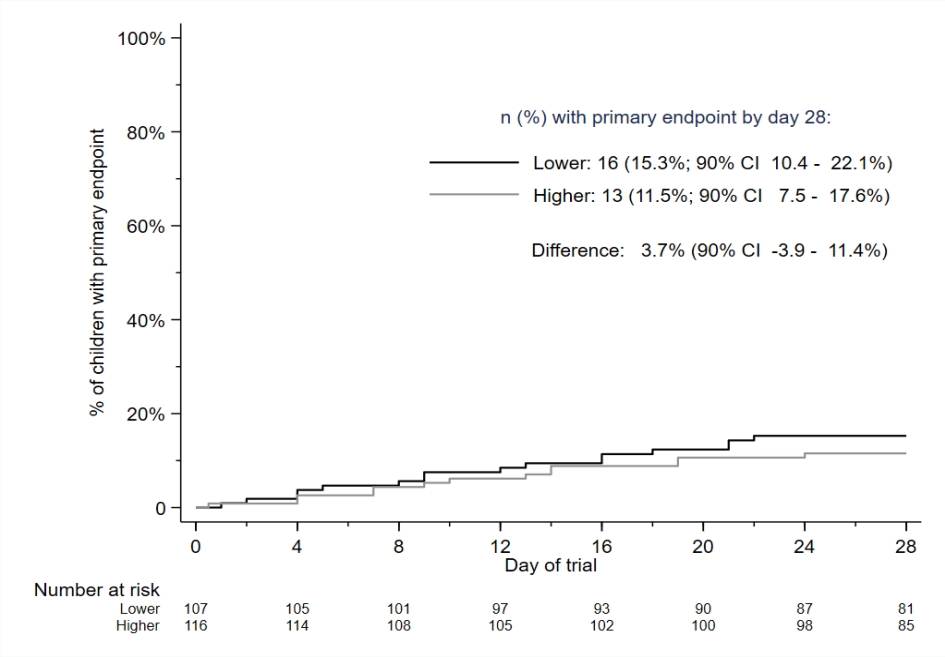
eFigure 6: Primary endpoint analysis for duration randomisation in PED pathway

Primary endpoint rates were 34/299 (11.5%) versus 37/292 (12.9%) in the 3-day and 7-day treatment groups (difference -1.4% (90%CI -5.8 to 3.1)). For children in the PED pathway, shorter treatment duration was therefore noninferior to longer treatment duration (eFigure 6).



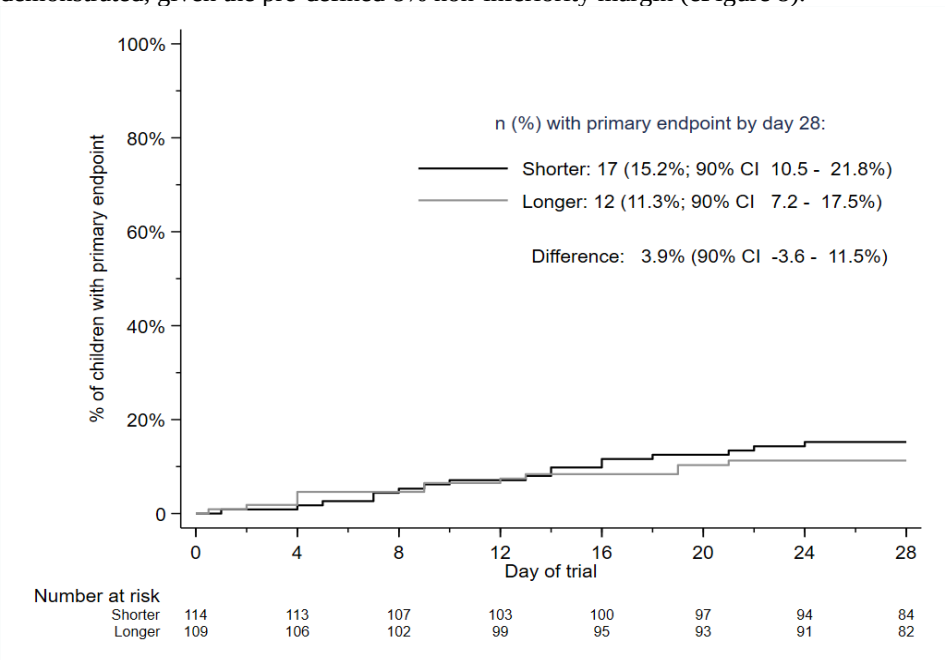
eFigure 7: Primary endpoint analysis for dose randomisation in WARD pathway

Among 223 children in the WARD pathway, primary endpoints occurred in 29 (13.3%) of children. Primary endpoint rates were 16/107 (15.3%) versus 13/116 (11.5%) participants in the lower dose and higher dose amoxicillin treatment groups (difference 3.7% (90%CI -3.9 to 11.4%)). For children in the WARD pathway with a much smaller sample size and consequent loss of statistical power, noninferiority of lower dose treatment to higher dose treatment therefore could not be demonstrated, given the pre-defined 8% non-inferiority margin (eFigure 7).



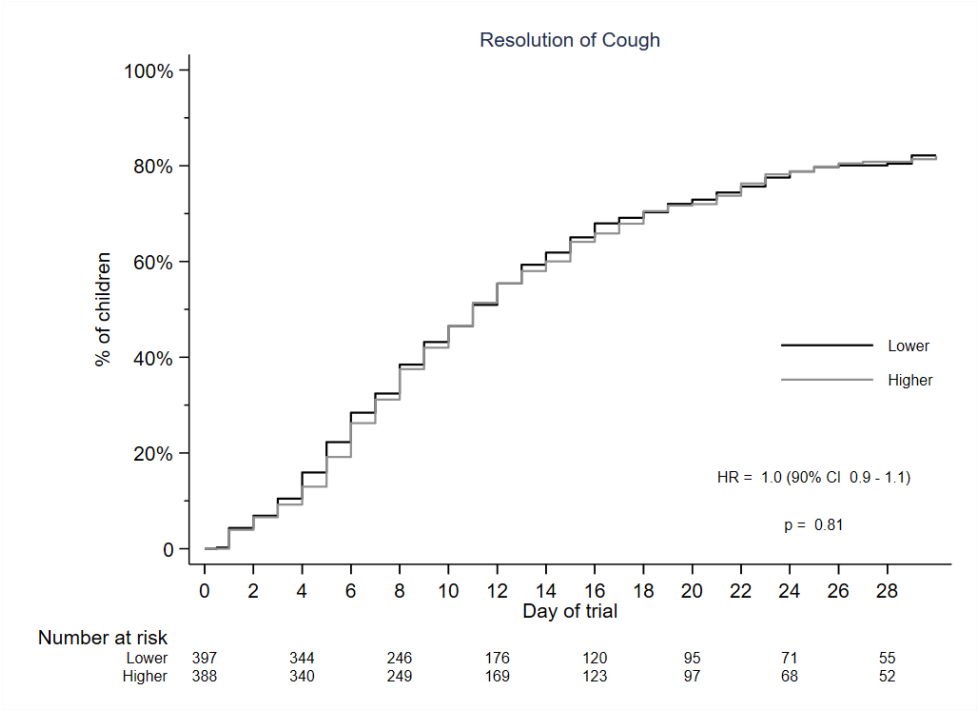
eFigure 8 Primary endpoint analysis for duration randomisation in WARD pathway

Primary endpoint rates were and 17/114 (15.2%) versus 12/109 (11.3%) in the 3-day and 7-day treatment groups (difference 3.9% (90%CI -3.6 to 11.5)). For children in the WARD pathway with a much smaller sample size and consequent loss of statistical power, noninferiority of shorter duration treatment to longer duration treatment therefore could not be demonstrated, given the pre-defined 8% non-inferiority margin (eFigure 8).

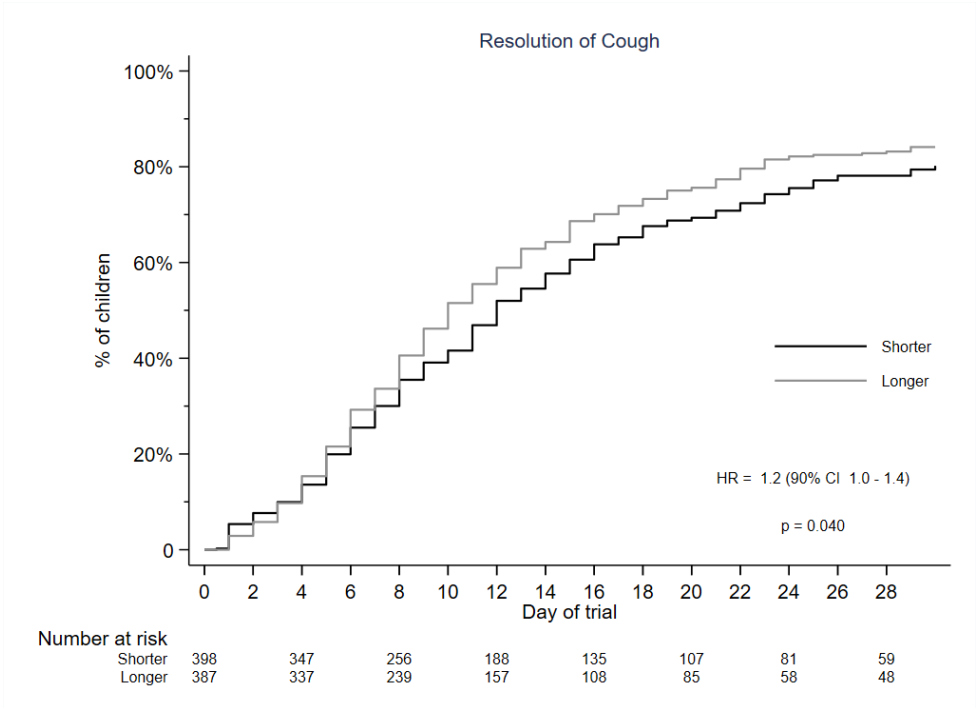


eFigures 9 a and b: Time to resolution of cough by randomisation group

a) Cough resolution: dose randomisation

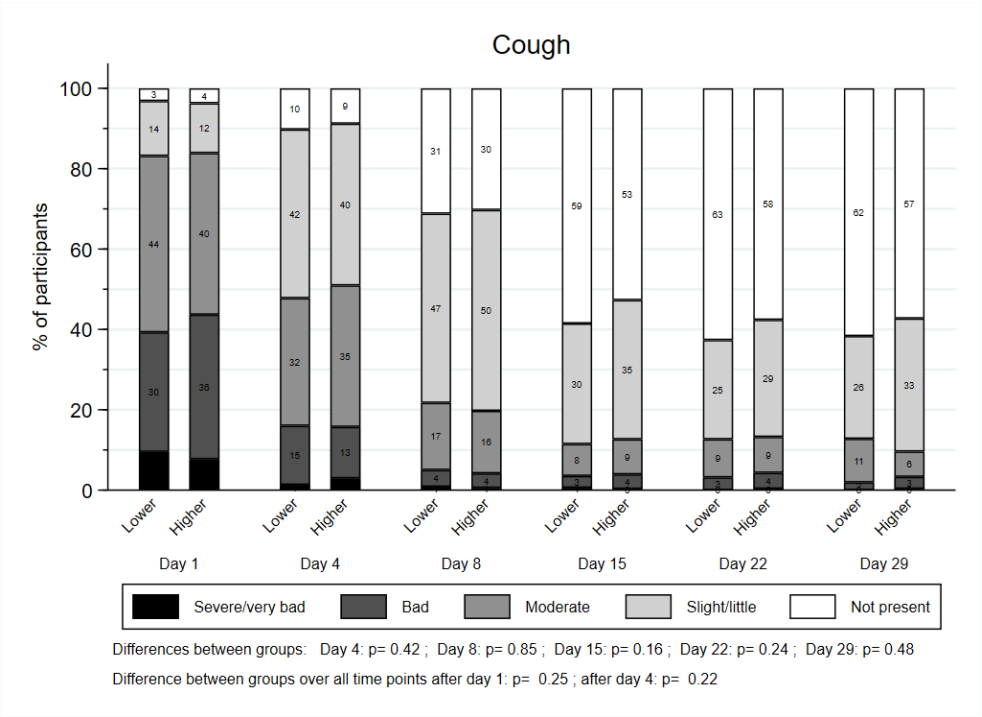


b) Cough resolution; duration randomisation

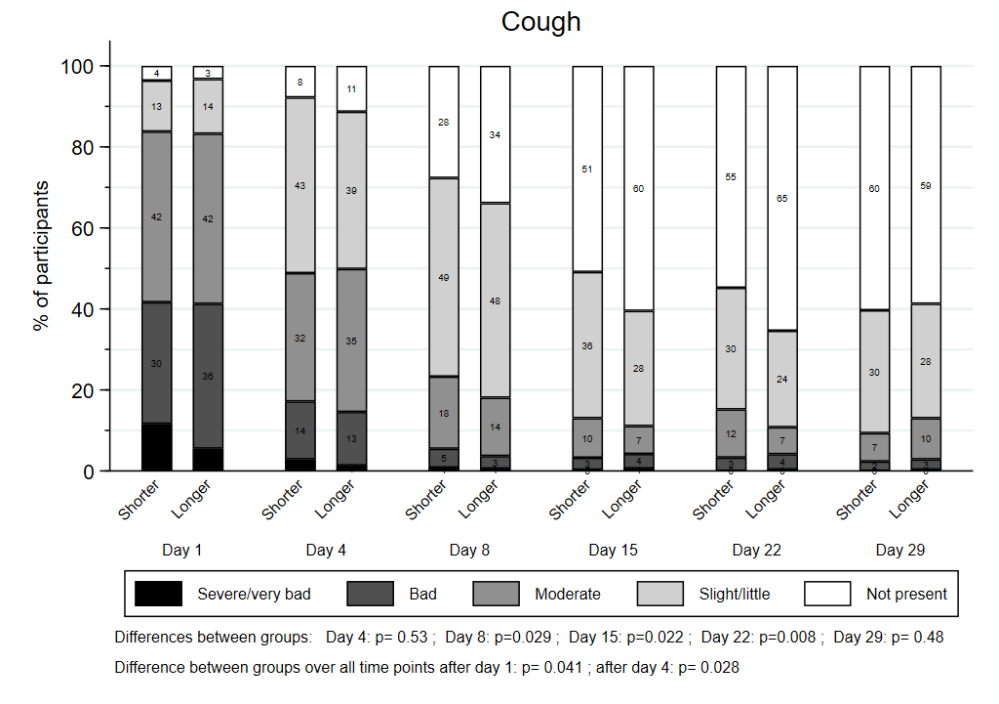


eFigures 10 a and b: Cough prevalence and severity by randomisation group and time point

a) Cough prevalence and severity: dose randomisation

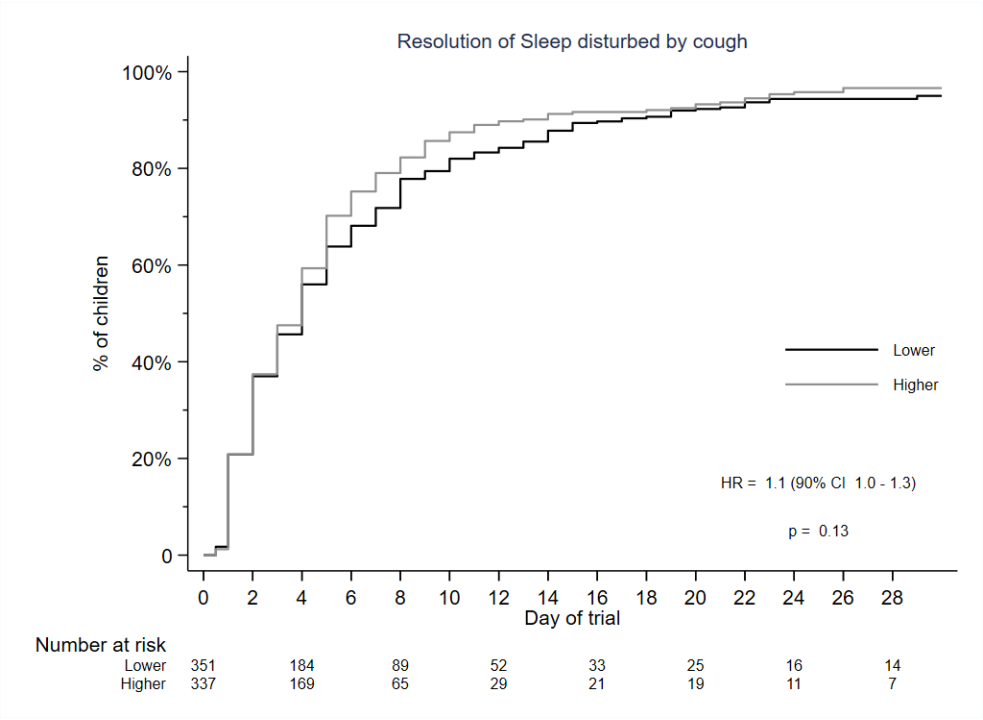


b) Cough prevalence and severity: duration randomisation

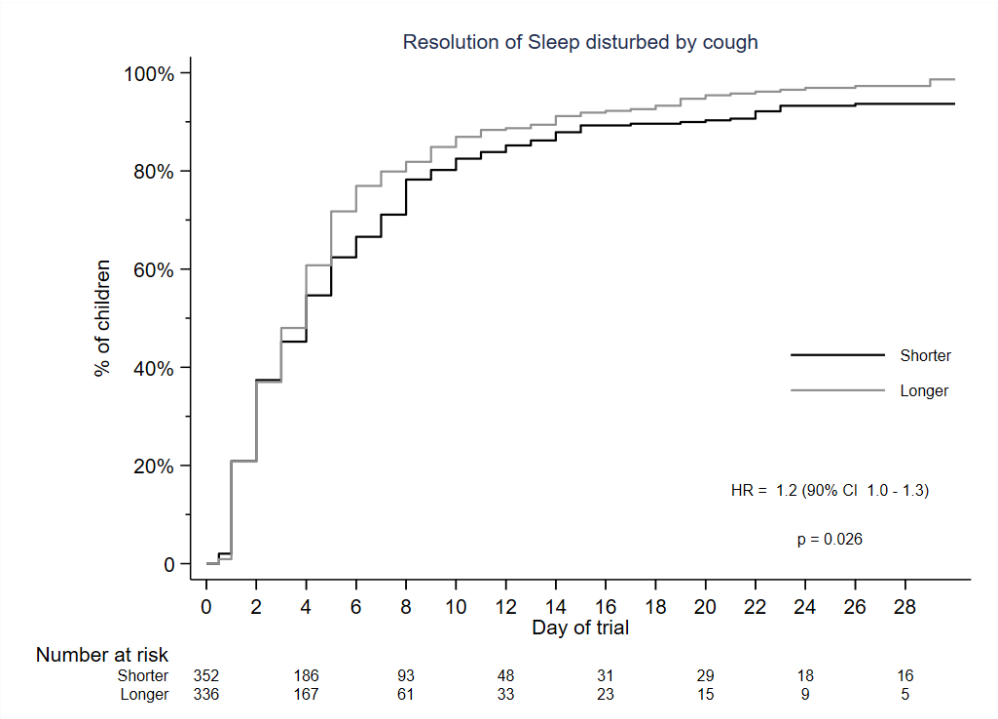


eFigures 11 a and b: Time to resolution of sleep disturbed by cough by randomisation group

a) Disturbed sleep resolution: dose randomisation

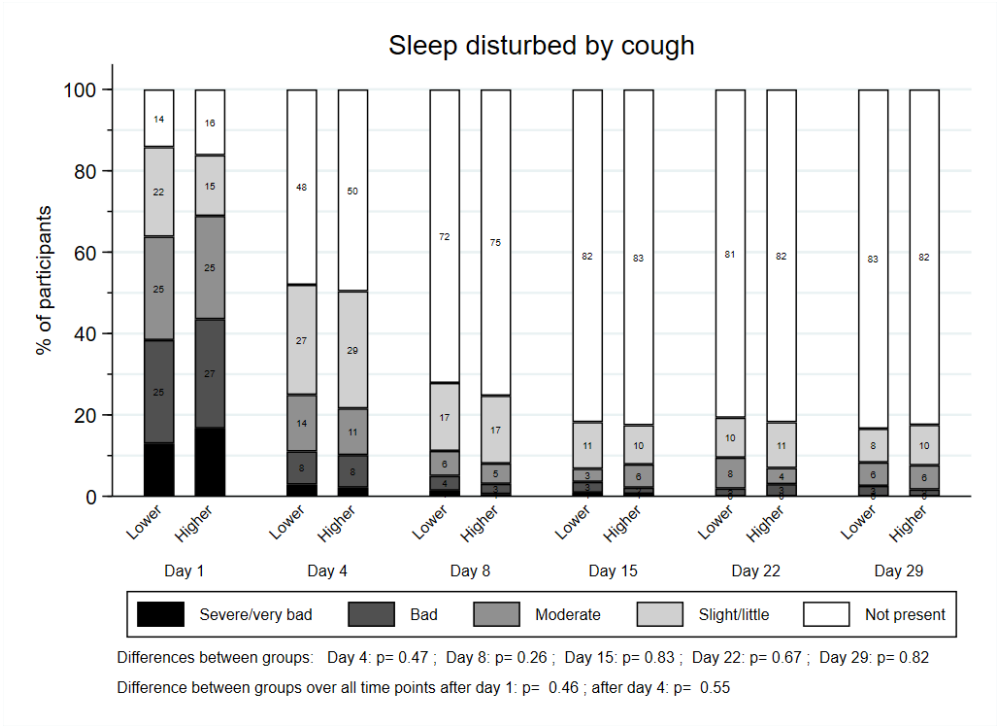


b) Disturbed sleep resolution: duration randomisation

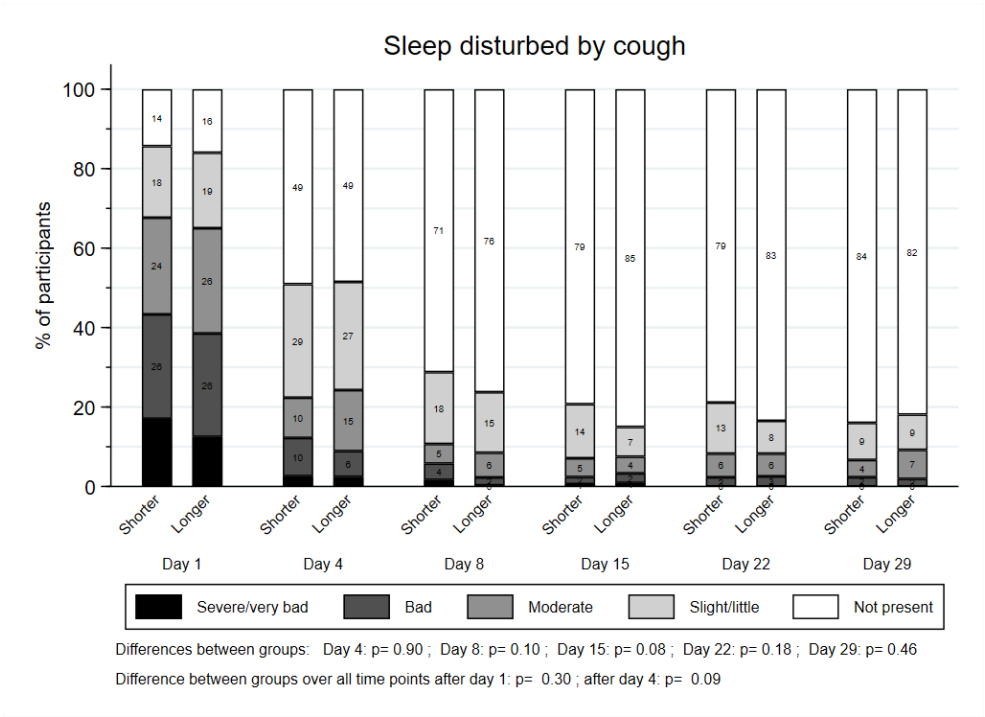


eFigures 12 a and b: Prevalence and severity of sleep disturbed by cough by randomisation group and time point

a) Disturbed sleep prevalence and severity: dose randomisation



b) Disturbed sleep prevalence and severity: duration randomisation



eTable 10: Adherence and adverse events, by 4 randomized groups

Outcome	Lower + shorter (n=208)	Lower + longer (n=202)	Higher + shorter (n=205)	Higher + longer (n=199)
Adherence: complete course taken				
All treatment [a]	173 (83.2%)	182 (90.1%)	185 (90.2%)	181 (91.0%)
Active treatment only [b]	201 (96.6%)	182 (90.1%)	203 (99.0%)	181 (91.0%)
Adherence: all doses taken and never smaller than prescribed volume				
All treatment [a]	146 (70.2%)	160 (79.2%)	154 (75.1%)	155 (77.9%)
Active treatment only [b]	192 (92.3%)	160 (79.2%)	195 (95.1%)	155 (77.9%)
Clinical possibly drug-related adverse events post enrolment				
Ever diarrhoea	97 (47.5%)	71 (35.9%)	90 (45.0%)	87 (45.8%)
Ever oral thrush	12 (5.9%)	15 (7.6%)	13 (6.5%)	17 (8.9%)
Ever skin rash	48 (23.5%)	46 (23.4%)	39 (19.5%)	60 (31.6%)
Serious adverse event, ever [c]	14 (6.7%)	9 (4.5%)	11 (5.4%)	9 (4.5%)

Note: a including non-adherence to placebo; b ignoring non-adherence to placebo; c No participant had more than one SAE, all SAEs were hospitalisations, no deaths.

eTable 11: S. pneumoniae and antimicrobial resistance on day 28, by 4 randomized groups

Outcome	**Lower + shorter** (n=208)	**Lower + longer** (n=202)	**Higher + shorter** (n=205)	**Higher + longer** (n=199)
Culture sample available	102/208 (57%)	122/202 (69%)	103/205 (60%)	110/199 (61%)
S. pneumoniae colonization	34/102 (33%)	32/122 (26%)	31/103 (30%)	32/110 (29%)
Penicillin MIC [a]				
0.016	9 (26%)	9 (28%)	6 (19%)	4 (13%)
0.032	18 (53%)	17 (53%)	18 (58%)	26 (81%)
0.064	0	1 (3%)	0	0
0.125	2 (6%)	2 (6%)	1 (3%)	0
0.25	4 (12%)	2 (6%)	4 (13%)	1 (3%)
0.5	0	0	1 (3%)	0
1	1 (3%)	1 (3%)	0	1 (3%)
2	0	0	1 (3%)	0
Penicillin-non-susceptibility [b] a) including all samples	7/102 (7%)	5/122 (4%)	7/103 (7%)	2/110 (2%)
b) in positive samples	7/34 (21%)	5/32 (16%)	7/31 (23%)	2/32 (6%)
Amoxicillin MIC [a]				
0.016	20 (59%)	22 (69%)	20 (65%)	23 (72%)
0.032	8 (24%)	6 (19%)	4 (13%)	7 (22%)
0.064	2 (6%)	2 (6%)	5 (16%)	0
0.125	1 (3%)	1 (3%)	0	0
0.25	2 (6%)	0	1 (3%)	1 (3%)
0.5	0	0	0	0
1	1 (3%)	1 (3%)	0	1 (3%)
2	0	0	1 (3%)	0
Amoxicillin-resistance/non-susceptibility [c] a) including all samples	1/102 (1%)	1/122 (1%)	1/103 (1%)	1/110 (1%)
b) in positive samples	1/34 (3%)	1/32 (3%)	1/31 (3%)	1/32 (3%)

Notes: a minimal inhibitory concentration. b Breakpoints for penicillin: MIC ≤ 0.064 mg/L = sensitive; MIC 0.125 to 2 mg/L = non-susceptible; MIC > 2 mg/L = resistant. c Breakpoints for amoxicillin: MIC ≤ 0.5 mg/L = sensitive; MIC >0.5 - 1 mg/L = non-susceptible; MIC > 1 mg/L = resistant

eTable 12: S. pneumoniae carriage

	Lower	Higher		Shorter	Longer		Total
			p-value			p-value	
Baseline Positive	133/327 (41%)	139/320 (43%)		132/317 (42%)	140/330 (42%)		272/647 (42%)
Final Visit Positive	66/224 (29%)	63/213 (30%)	0.98	65/205 (32%)	64/232 (28%)	0.35	129/437 (30%)
Summary: pneumococcal carriage *	n=194	n=182		n=171	n=205		n=376
Never	93 (48%)	72 (40%)		76 (44%)	89 (43%)		165 (44%)
Baseline only	46 (24%)	54 (30%)		39 (23%)	61 (30%)		100 (27%)
Final visit only	21 (11%)	20 (11%)		20 (12%)	21 (10%)		41 (11%)
Both	34 (18%)	36 (20%)		36 (21%)	34 (17%)		70 (19%)

Notes: *patients with culture results at both time-points.

eTable 13: Penicillin non-susceptibility in patients with available culture result (positive or negative)

	Lower	Higher		Shorter	Longer		Total
			p-value			p-value	
Baseline	25/327 (8%)	21/320 (7%)		24/317 (8%)	22/330 (7%)		46/647 (7%)
Final visit	12/224 (5%)	9/213 (4%)	0.58	14/205 (7%)	7/232 (3%)	0.063	21/437 (5%)
Summary: Penicillin non-susceptibility *	n=194	n=182		n=171	n=205		n=376
Never	175 (90%)	166 (91%)		151 (88%)	190 (93%)		341 (91%)
Baseline only	10 (5%)	9 (5%)		9 (5%)	10 (5%)		19 (5%)
Final visit only	6 (3%)	3 (2%)		6 (4%)	3 (1%)		9 (2%)
Both	3 (2%)	4 (2%)		5 (3%)	2 (1%)		7 (2%)

eTable 14: Penicillin non-susceptibility in patients with a culture positive for S. pneumoniae

	Lower	**Higher**		**Shorter**	**Longer**		**Total**
			p-value			p-value	
Baseline	25/133 (19%)	21/139 (15%)		24/132 (18%)	22/140 (16%)		46/272 (17%)
Final visit	12/66 (18%)	9/63 (14%)	0.55	14/65 (22%)	7/64 (11%)	0.10	21/129 (16%)
Summary: **Penicillin non-susceptibility ***	n=34	n=36		n=36	n=34		n=70
never	24 (71%)	31 (86%)		26 (72%)	29 (85%)		55 (79%)
Baseline only	3 (9%)	0 (0%)		2 (6%)	1 (3%)		3 (4%)
Final visit only	4 (12%)	1 (3%)		3 (8%)	2 (6%)		5 (7%)
Both	3 (9%)	4 (11%)		5 (14%)	2 (6%)		7 (10%)

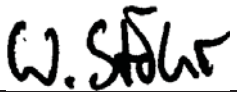
CAP-IT

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

ISRCTN #: 76888927; EUDRACT #: 2016-000809-36
CTA #: 17141803; REC #: 16/LO/0831

STATISTICAL ANALYSIS PLAN

Version 2.0, 2-Dec-2020

Author	Position	Signature	Date
Wolfgang Stöhr	Trial Statistician		3. Dec 2020
Approved by	**Position**	**Signature**	**Date**
David Dunn	Trial Statistician		2. Dec 2020
Mike Sharland	Chief Investigator		2. Dec 2020

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

TABLE OF CONTENTS

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

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Supplemental Online Content: Nonauthor Collaborators

*Indicates required information. Only first name, last name, and suffix will appear in PubMed.

***Group Name(s): Trial Steering Committee (TSC), Independent Data Monitoring Committee (IDMC), Independent Endpoint Review Committee (ERC), Trial Management Group (TMG), Investigators**							
***First Name and Middle Initial(s)**	***Last Name**	***Suffix (eg, Jr, III)**	Academic Degrees	Institution	Location (city, state/province, country)	Role or Contribution, eg, chair, principal investigator	Group (if more than 1 Group listed in the byline) and/or Subgroup (eg, Steering Committee)
TSC							
Elizabeth	Molyneux			College of medicine, Blantyre Malawi	UK	Chair	TSC
Chris C	Butler			Nuffield Department of Primary Care Health Sciences, University of Oxford	Oxford, UK		TSC
Alan	Smyth			Professor of Child Health, University of Nottingham	Nottingham	Steering committee member	TSC
Catherine	Prichard						TSC
IDMC							
Tim E.A	Peto						IDMC
Simon	Cousens			London School of Hygiene and Tropical Medicine	London		IDMC
Stuart	Logan			University of Exeter Medical School	Exeter, Devon		IDMC
ERC							
Alasdair	Bamford			Great Ormond Street Hospital for Children NHS Foundation Trust	London	ERC member	ERC
Anna	Turkova			MRC CTU at UCL; Great Ormond Street Hospital	London, UK	ERC member	ERC
Anna L	Goodman						ERC
Felicity	Fitzgerald			UCL Great Ormond Street Institute of Child Health	London, UK	ERC	ERC
TMG							
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Supplemental Online Content: Nonauthor Collaborators

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***First Name and Middle Initial(s)**	***Last Name**	***Suffix (eg, Jr, III)**	Academic Degrees	Institution	Location (city, state/province, country)	Role or Contribution, eg, chair, principal investigator	Group (if more than 1 Group listed in the byline) and/or Subgroup (eg, Steering Committee)
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Louise	Rogers						TMG
Elia	Vitale						TMG
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Poonam	Patel					Co-Principal Investigator	PERUKI
Hannah	Fletcher					Nurse	
Kribashnie	Nundlall					Nurse	

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Jamie	Carungcong					Nurse	
Rhian	Bull					Nurse	
Nabila	Burney					Nurse	
Patricia	Correia Da Costa					Nurse	
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Beth	Walton					Nurse	
Alice	Smith					Nurse	
Michelle	Ross					Nurse	
Lucie	Aplin					Nurse	
Sarah	Sheedy					Nurse	
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Jeff	Morgan					Principal investigator	PERUKI
Jennifer	Muller					Nurse	
Gail	Marshall					Nurse	
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Sarah	Giwa			Evelina London Children's Hospital		Nurse	
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Tanya K Z	Baron					Co-PI	PERUKI
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Sally	Beer					Nurse	
Maria Jose	Garcia Garcia					Nurse	
Dom	Georgiou					Nurse	
Kirsten	Beadon					Nurse	
Jose	Martinez						
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Hannah	Cotton						
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Lizzie	Starkey					Co-PI	GAPRUKI
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Alice	Downes						

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Ellen	Barry					Nurse	
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Helen	Bannister					Nurse	
Ben	Bloom					PI	PERUKI
Ami	Parikh					Co-PI	PERUKI
Imogen	Skene					Nurse	
Helen	Power					Nurse	
Olivia	Boulton					Nurse	
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Jonathon	Walters						
Daniel	Martin						
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Katherine	Potier						
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Emma	Gardiner					Nurse	
Katrina	Cathie					PI	GAPRUKI
Jane	Bayreuther					Co-PI	PERUKI
Ruth	Ensom					Nurse	
Emily K	Cornish					Nurse	
Elizabeth-Jayne L	Herrieven					PI	PERUKI
William	Townend					Co-PI	PERUKI
Leanne	Sherris					Nurse	
Paul	Williams					Nurse	

Data Sharing Statement

Data
Data available: Yes
Data types: Other (please specify)
Additional Information: Data will be shared according to the Medical Research Council Clinical Trials Unit's controlled access approach, based on the following principles: No data should be released that would compromise an ongoing trial or study.
How to access data: jbielick@sgul.ac.uk
When available: With publication

Supporting Documents
Document types: Other (please specify)
Additional Information: Standard Operating Procedure for data sharing from the Medical Research Council Clinical Trials Unit
How to access documents: jbielick@sgul.ac.uk
When available: With publication

Additional Information
Who can access the data: Please see statement above.
Types of analyses: Please see statement above.
Mechanisms of data availability: Please see statement above.
Any additional restrictions: Please see statement above.