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 3.0
Date: 1st September 2017

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

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

Authorised by:
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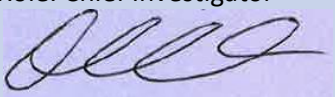

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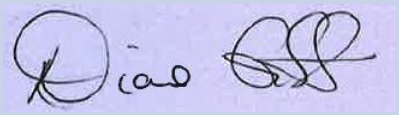

GENERAL INFORMATION

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 (DPA number: Z6364106), 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 Max Parmar, MRC CTU at UCL Director, Institute of Clinical Trials and Methodology, MRC CTU at UCL, Aviation House, 125 Kingsway, London, WC2B 6NH or via the trial team. From 22nd September 2017 the MRC CTU address will be 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 fax a completed SAE form to the MRC CTU at UCL on:
Fax: 020 7670 4814 or 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
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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	V3.0
Date	30Aug2017
UCL ID	16/0172
ISRCTN #	ISRCTN76888927
EudraCT #	2016-000809-36
CTA #	17141803
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. Children will be enrolled from Paediatric Emergency Departments (PEDs), Paediatric Assessment Units (PAUs) and inpatient wards at CAP-IT trial sites.
Type of Participants to be Studied	Children aged greater than 6 months, weighing 6 - 24 kg presenting to PED or PAU or admitted to inpatient wards in the UK with a clinical diagnosis of CAP in whom the decision has been made to treat with antibiotics.
Setting	CAP-IT aims to recruit children from 2 different settings: 1. PED Group: children who are recruited in the Paediatric Emergency Department or PAU. Children in this group will be treated at home with antibiotics and may be entered into the trial prior to receiving any antibiotic prescription OR after having received ≤48 hours of beta-lactam treatment as an outpatient. The CAP-IT study drug will be started on discharge. 2. WARD Group: children who are recruited from inpatient paediatric hospital wards or from PAU. Children in this group will receive ≤48 hours of antibiotic treatment (oral or IV beta-lactam therapy) on the ward, or in PAU, prior to entering the CAP-IT trial. The CAP-IT study drug will be started on discharge.
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

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	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(s)	Any systemic antibacterial treatment prescribed in addition to the allocated trial medication as an inpatient or outpatient up to and at final follow-up 4 weeks after randomisation. This includes re-treatment, extension of treatment and treatment with additional antibiotics.
Secondary Outcome Measure(s)	Specified clinical adverse events (including thrush, skin rashes and diarrhoea), severity and duration of parent-reported CAP symptoms, health economics, cumulative number of additional courses of antibiotics and total number of days of re-treatment, adherence and penicillin resistance.
Randomisation	Children will be randomised separately according to whether they are enrolled in the PED or WARD group (see 'Setting' above).
Number of Participants to be Studied	2400 recruited over 2 years
Duration	Children will be recruited over a period of 2 years and will be followed up for 28 days. There will be a 3 month internal pilot during the first winter season.
Ancillary Studies/Substudies	• Impact on gastrointestinal microflora • Detection of respiratory bacteria and viruses in blood
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. PED Group - Trial Entry, Randomisation and Treatment

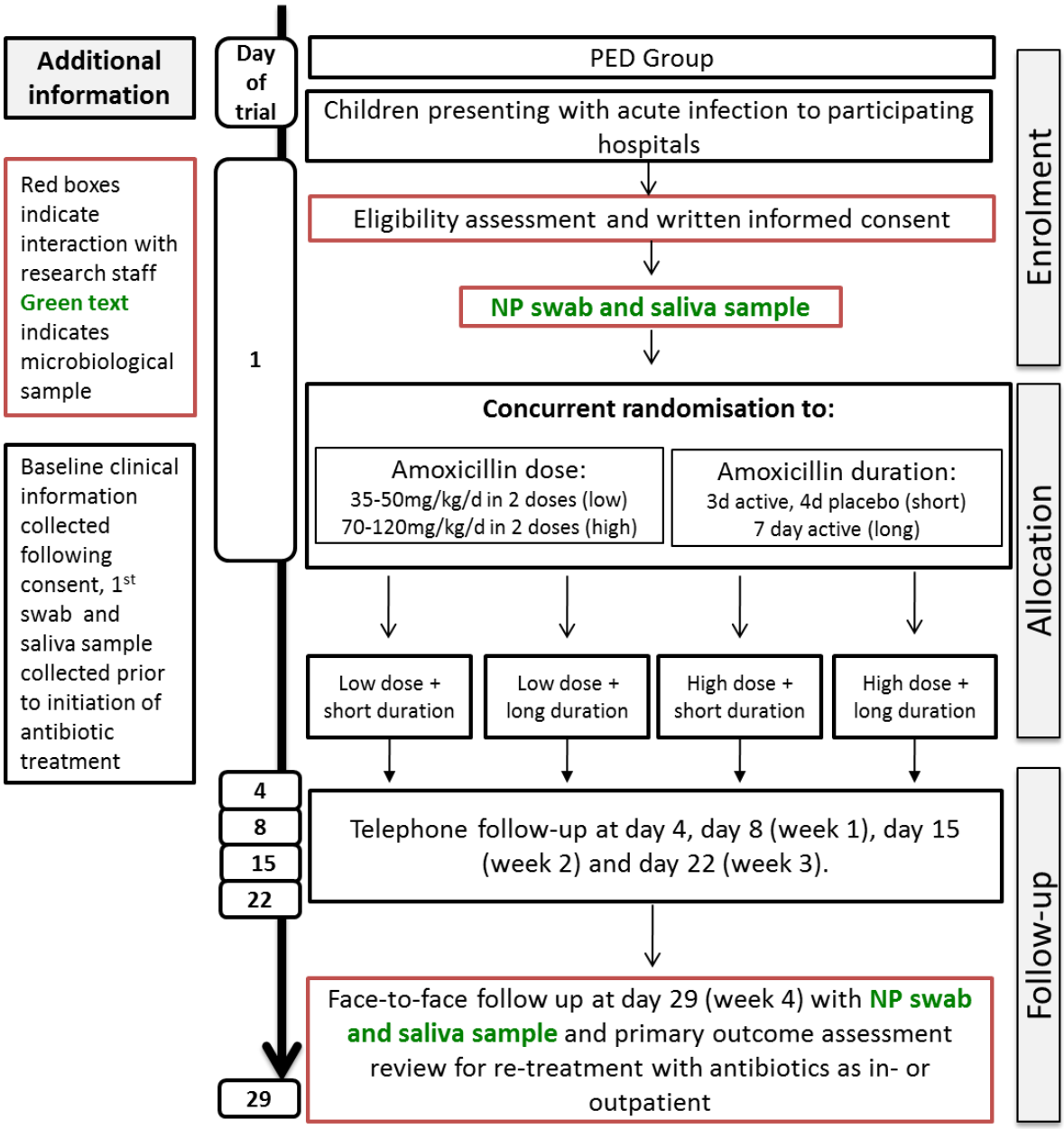
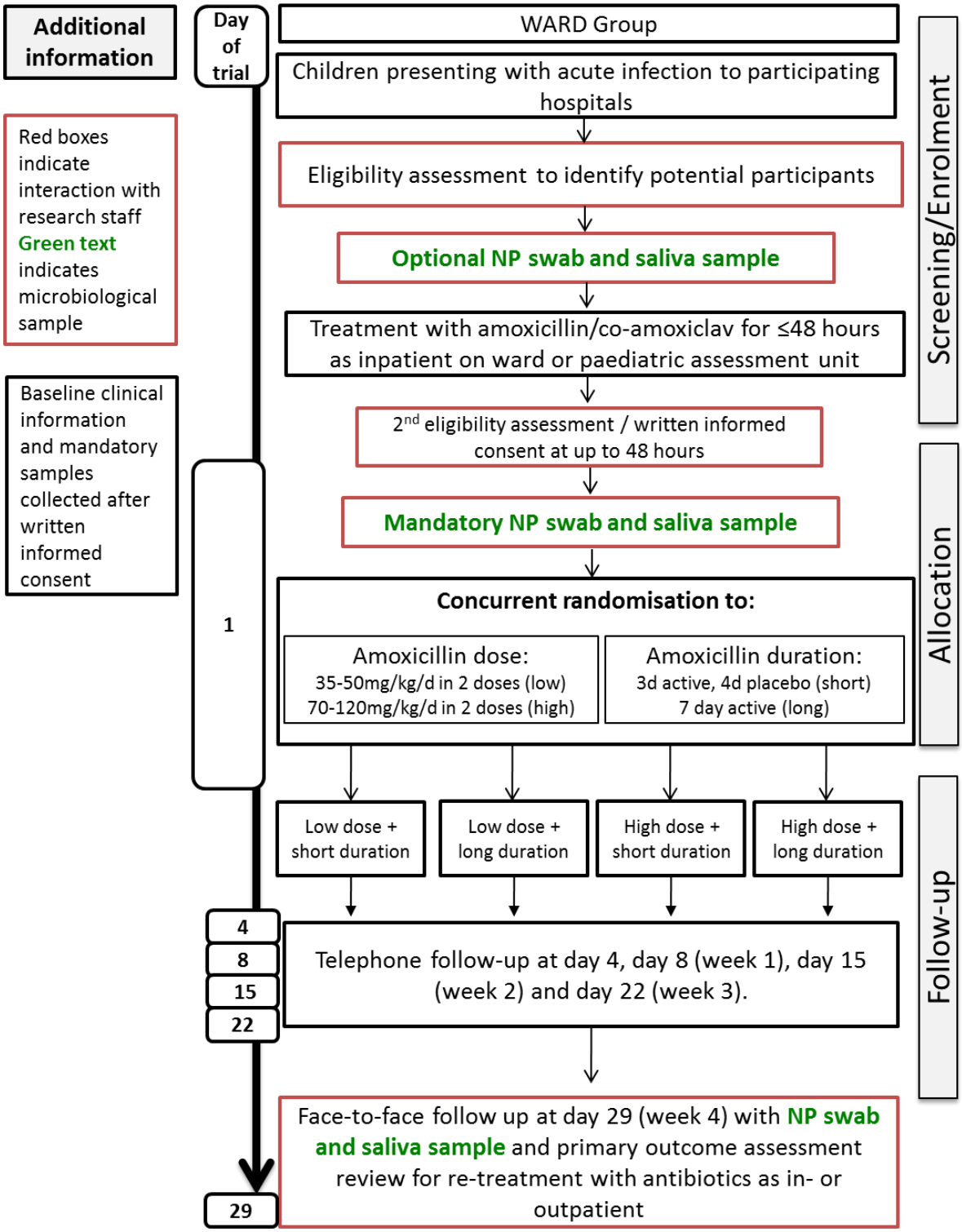


Figure 2. WARD Group – Trial Entry, Randomisation and Treatment



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 questionnaire[a]		X	X				(X)[b]
	Adherence review (returned 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	X
	Laboratory assessment							
	Nasopharyngeal swab[g]	X					X	(X)
	Saliva sample[h]	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	
	Blood sample[n]	X[n]						

(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, 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 current saliva sampling kit can be used at site, a saliva sample should be collected prior to 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.
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.

Investigations to be carried out only in a subset of children at selected sites

m. Sample should be collected as close as possible to randomisation (within 24 hours after randomisation). Please refer to the CAP-IT sample collection manual for details of collection and postage.
n. EDTA blood samples (minimum volume 500µl) will be opportunistically obtained during routine phlebotomy from 50 children in whom a blood culture is also taken. Please refer to the CAP-IT sample collection manual for details of collection and storage of blood samples.

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[a]	X							
	Informed consent[a]		X						
	Drug supply dispensing		X						
	Adherence questionnaire[b]			X	X				(X)[c]
	Adherence review (returned 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
	EQ-5D[g]		X	X	X			X	(X)
	Use of health services[b]		X[h]	X	X	X	X	X	X
	Laboratory assessment								
	Nasopharyngeal swab[i]	(X)	X					X	(X)
	Saliva sample[j]	(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-studies								
	Stool sample	X[o]	[o]					X	
	Blood sample[p]	X[p]	[p]						

(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 and saliva samples, 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. Modified EQ-5D (wellbeing questionnaire) to be completed by parents at baseline, day 4, day 8, day 29 and if an acute event takes place.
h. Data collection on healthcare use during hospitalisation from medical record including record of antibiotic and other supportive treatment up to the time of randomisation.
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 current saliva sampling kit can be used at site, a saliva sample will be collected at randomisation and, if possible, prior to child starting antibiotic treatment. Deferred written informed consent will be sought for samples collected prior to formal enrolment in CAP-IT. Saliva samples will also be taken 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.
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.

Investigations to be carried out only in a subset of children at selected sites

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.
p. EDTA blood samples (minimum volume 500µl) will be opportunistically obtained during routine phlebotomy from 50 children. Please refer to the CAP-IT sample collection manual for details of collection and storage of blood samples.

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
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
PCV	Pneumococcal Vaccination

Abbreviation	Expansion
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
SSG	Scientific Strategy Group

Abbreviation	Expansion
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. 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 inpatient paediatric hospital wards or paediatric assessment units (PAUs). Children in this group will receive ≤48 hours of inpatient treatment with any beta-lactam antibiotic prior to entering the trial.

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.

During the early part of the study, participating centres will be asked to keep anonymised 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. The screening log may be extended to the main trial if found to be practicable and informative.

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 in last 96 hours) AND
   - Temperature ≥38^{o}C measured by any method OR likely fever in last 48 hours 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
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 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 as inpatient 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	Altered mental state (Glasgow Coma Score<14 or AVPU scale <A)	Empyema Pleural effusion

Hypotension as defined by Advanced Paediatric Life Support/European Paediatric Life Support guidelines	Requirement for invasive ventilation or non-invasive ventilatory support	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 should 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 and saliva sample (these samples will be collected at randomisation following informed consent). Every effort should be made to collect these samples however if for any reason it is not possible to obtain the nasopharyngeal swab and/or saliva sample, the child can still be included in the trial.
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:

8. Haematology: haemoglobin, platelet count, leukocyte count, neutrophil count, lymphocyte count
9. Biochemistry: C-reactive protein, procalcitonin and electrolytes
10. Virology: 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-studies (and where additional consent is given):

12. Stool sample
13. Blood 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 after an initial period of up to 48 hours of antibiotic treatment as inpatients on the WARD or in a PAU.

3.2.1 NASOPHARYNGEAL SWAB AND SALIVA SAMPLE

The nasopharyngeal swab and the saliva sample (for those sites able to use saliva sample kits) 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 and saliva sample 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 and saliva sample 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.

Please refer to **Figure 2**.

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.

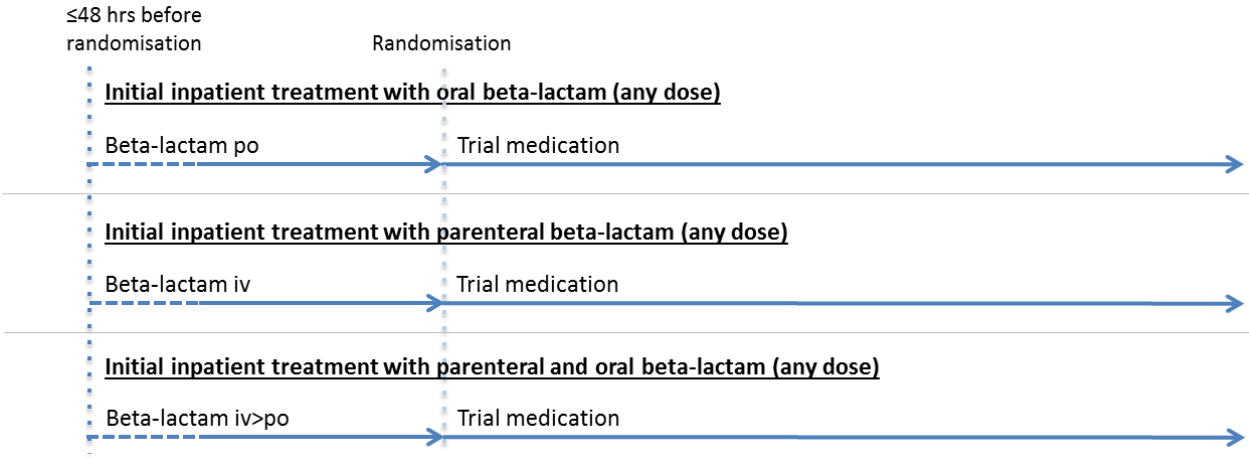
Written informed consent will be obtained from parents/guardians after explanation of the aims, methods, benefits and potential hazards of the trial and **before** randomisation. It must be made completely and unambiguously clear that the parent/guardian of a child is free to refuse to participate in 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 in last 96 hours) AND;
    - Temperature ≥38^{o}C measured by any method OR likely fever in last 48 hours 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
3. Admitted to a paediatric assessment unit or inpatient ward at a participating hospital
4. Treated with any oral or intravenous beta-lactam for ≤48 hours after admission (see **Figure 3**)
5. Decision to further treat with oral amoxicillin for CAP on discharge from hospital
6. Child is considered fit for dischargeat time of randomisation
7. 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
8. Parent/guardian willing to accept all possible randomised allocations
9. Informed consent for trial participation signed by a parent/guardian

Figure 3. Acceptable antibiotic treatment during ≤48 hours after admission in WARD group



3.2.4 EXCLUSION CRITERIA

1. Severe underlying chronic disease 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. Already on systemic antibiotic treatment at presentation
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 antibiotic other than a beta-lactam during admission
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 inpatient antibiotic treatment
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 and saliva sample (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-studies (and where additional consent is given):

12. Stool sample
13. EDTA blood sample (if possible both before start of inpatient antibiotic treatment and at randomisation)

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 which group the child is joining).

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**).

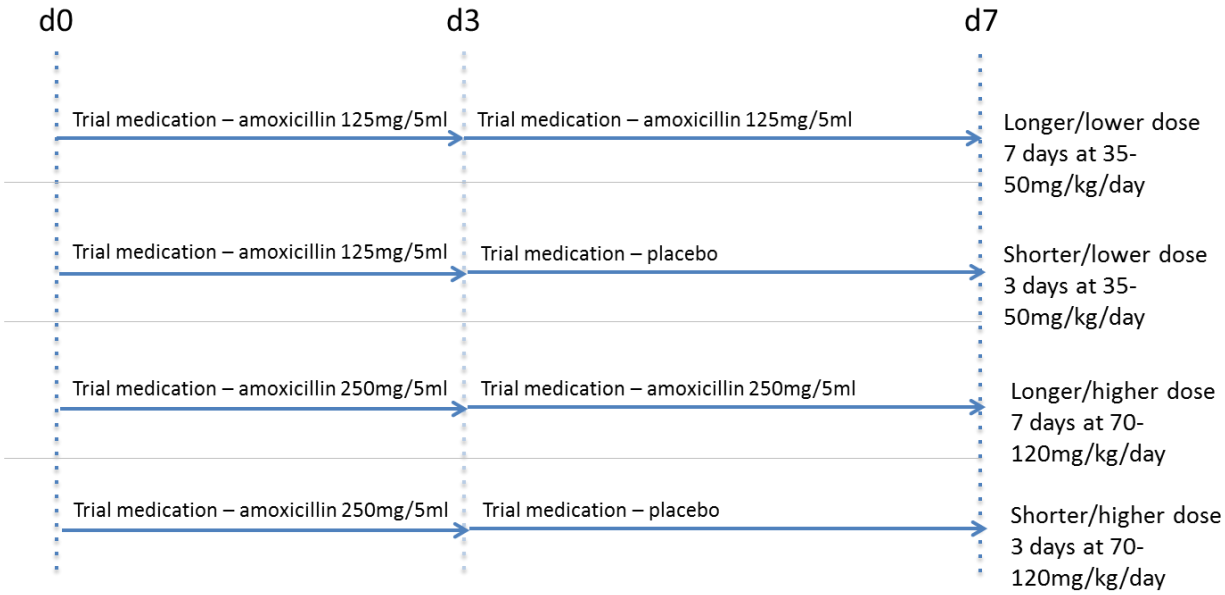
5.2.2 RANDOMISATION 2 (R2): DURATION OF ORAL AMOXICILLIN

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 4** below.

Figure 4. 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 IMP 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 <17kg, 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, 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.

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 in the trial SOP. Emergency unblinding procedures can be found on the CAP-IT website (www.capitstudy.org.uk) and in the CAP-IT Manual of Operations (MOP).

5.8 NON-TRIAL TREATMENT

5.8.1 MEDICATIONS PERMITTED

All necessary concomitant medications are allowed. Regular medications will be recorded at enrolment. 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 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. Baseline nasopharyngeal samples will also be screened for the presence of a panel of common respiratory viruses using molecular techniques (PCR).

6.2.2 SALIVA SAMPLES

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^{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. The saliva samples will be locally stored frozen, ideally at -80^{o}C (-20^{o}C is acceptable where no -80^{o}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 and at final follow-up from 200 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.

The baseline sample will be collected prior to treatment with antibiotics or as soon as possible after initiation of antibiotics. Samples can be taken at home using a custom-made collection kit, which has been evaluated for use in young children. Secure freepost pre-addressed envelopes will be made available. All samples will be processed, frozen and stored at the central laboratory (Institute of Child Health, UCL) according to a predefined laboratory protocol.

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

6.3.1 EDTA SAMPLE (SUBSTUDY IN A SUBSET OF PARTICIPANTS)

An additional small volume (minimum volume 500µl) of blood (EDTA) will be collected in a sample of 50 participants undergoing routine phlebotomy at the discretion of the managing physician at baseline to assess whether respiratory pathogens can be detected in blood using a panel of molecular assays. Samples would ideally be taken before antibiotics have been administered. Samples will be processed, frozen and stored locally and then transferred to a central laboratory (Institute of Child Health, UCL) in batches for processing and storage according to a predefined laboratory protocol.

6.4 ADHERENCE AND ACCEPTABILITY

All parents/guardians will be asked to complete an adherence and acceptability questionnaire and will be asked to return any unused medication at final follow-up. Parent/guardian responses to the adherence questionnaire 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.

Parents/guardians will also be asked to complete quality of life questionnaires (EQ-5D adapted for use in the paediatric population) at randomisation, day 4, day 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 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.

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 section6section 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 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 IMP 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 hospital number 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) will be followed.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Children will be randomised separately according to whether they are enrolled in the PED or 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:

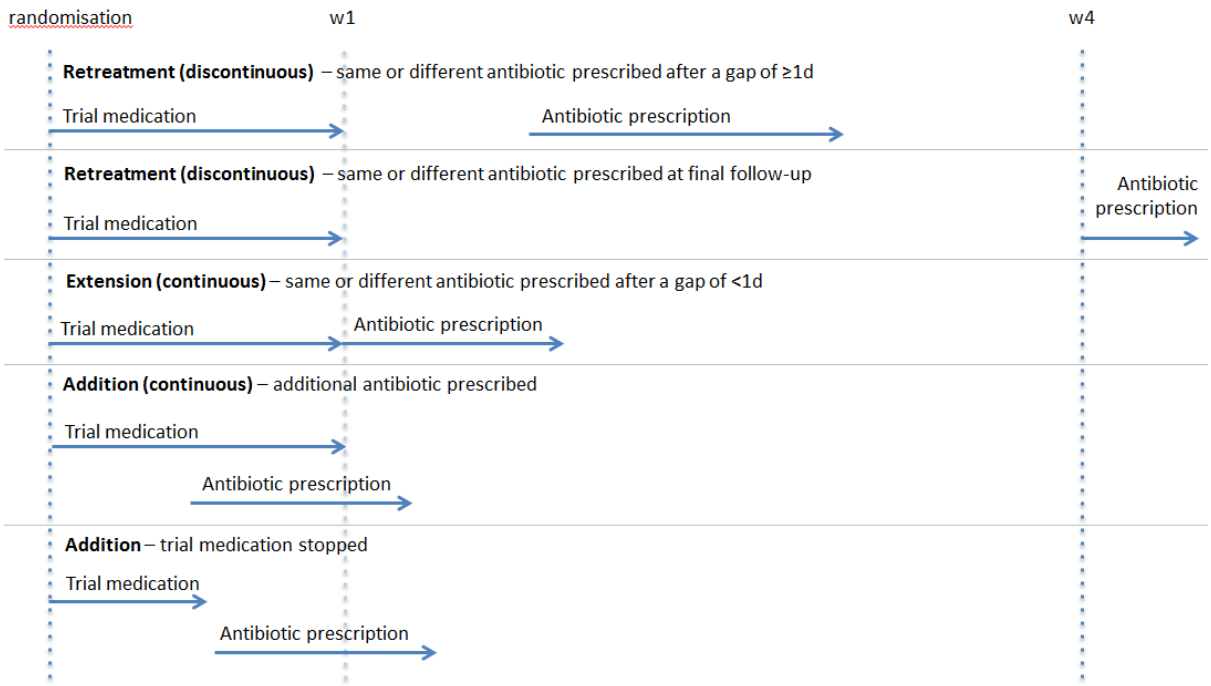
1. To determine whether lower dose (35-50mg/kg/day) oral amoxicillin treatment is non-inferior to higher dose (70-90mg/kg/day) amoxicillin treatment for uncomplicated childhood CAP as determined by additional/subsequent antibiotic treatments.
2. To determine whether shorter duration (3 days) amoxicillin treatment is non-inferior to longer duration (7 days) amoxicillin treatment for uncomplicated childhood CAP as determined by additional/subsequent antibiotic treatment.

9.3 OUTCOME MEASURES

9.3.1 PRIMARY OUTCOME MEASURE

The primary outcome is defined as any systemic antibacterial treatment in addition to the allocated trial medication as an inpatient or outpatient up to and including week 4 final follow-up. This includes re-treatment, increase in amoxicillin dose, extension of treatment and treatment with additional agents (see **Figure 5**).

Additional antibiotic treatment within 4 weeks from randomisation considered to represent a primary outcome measure event



The use of blinding will provide protection against ascertainment bias.

9.3.2 Secondary Outcome measures

9.3.2A Morbidity:

- Specified clinical adverse events, including thrush, skin rashes and diarrhoea.
- Severity and duration of parent/guardian-reported CAP symptoms.
- Number of days off work for parents/guardians and number of days away from out-of-home child care (where relevant).

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.

9.3.2D Other:

- Cumulative number of additional courses of antibiotics and total number of days of re-treatment with antibiotics.

9.3.3 Health-economic outcomes

- Quality of life (using EQ-5D adapted for use in the paediatric population)
- Cost-causing events and associated resource use including
  - Costs based on patient admission and discharge dates
  - Treatment costs
  - Costs associated with treatment failure such as re-admissions and re-treatments

9.4 SAMPLE SIZE

WARD and PED groups will be analysed separately (see **Section 9.5**). 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 assumed underlying antibiotic re-treatment rate is 5% (see **Section 1**). The same value has been assumed for WARD and PED; although WARD group includes children with more severe CAP who may be more likely to relapse, this is expected to be counter-balanced by the additional up to 2 days of oral or IV antibiotic treatment prior to randomisation. Assuming a 5% event rate, 4% non-inferiority margin assessed against an upper 1-sided 95% CI, 90% power, and 15% loss to follow-up 1,200 children need to be randomised to each of WARD and PED groups. The total sample size is therefore 2,400 children. These assumptions will be reviewed at the end of the pilot phase (see below) by the IDMC/TSC, which may result in a re-estimation in the sample size.

9.5 INTERIM MONITORING & ANALYSES

An IDMC Charter will be drawn up that 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 will specify 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 PILOT PHASE

The study incorporates an internal pilot phase covering 3 months during the first winter season of recruitment. Recruitment will not halt after the pilot phase but the IDMC/TSC will be asked to review recruitment rates relative to pre-specified targets. They will also give particular consideration to the overall rate of the primary endpoint (blinded to intervention arm), and to data on completion of follow-up, attendance at week 4 visits in particular, adherence and acceptability of collecting microbiological samples, with the aim of confirming that the trial remains viable with the planned recruitment targets and timelines. The IDMC will make recommendations to the TSC and TMG regarding continuation of the trial, and may choose to release some of the data to them if appropriate.

9.7 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 separately. However, the interpretation of the findings will consider both strata together as the same qualitative effects are expected. The primary analysis will be intention-to-treat (ITT), with all participants analysed according to the group to which they were randomised regardless of treatment actually received. The primary endpoint will be analysed using standard methods for comparing proportions (chi^2 test; generalised linear model with binomial

outcome and identity link; logistic regression). A test of interaction will be conducted between the effects of dose and duration; main effects will be estimated only if this test is non-significant.

The primary analysis of the primary endpoint will include all reasons for additional antibacterial treatment. However, sensitivity analyses will be performed excluding reasons (e.g. non-tolerability of IMP) that are unlikely to be related to resolution/prevention of relapse of lower respiratory illness. Another subgroup analysis will consider the severity of CAP at presentation (for example, based on radiological and surrogate biomarker data; details to be defined in the Analysis Plan), 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 "contamination" of the study population by children with mild disease of viral aetiology.

As it is widely accepted that inference should be based primarily on point estimates and confidence intervals rather than significance tests, the interpretation will emphasise the observed data rather than a 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.

9.8 HEALTH-ECONOMIC ANALYSES

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.

Health economic analyses will make use of three main modelling methodologies: Firstly, a decision analytic model will be used to conduct the basic cost-effectiveness analysis of the trial with a decision node and four branches representing the four alternative treatment protocols, each with associated treatment regimen costs and outcomes.

Secondly, to perform an initial analysis to attempt to quantify the impact of resistant strains, a time-dependent multi-state mode will be developed. This model will analyse trial data to estimate daily probabilities of discharge and death, in both children colonised with sensitive strains and those colonised with resistant strains (at the beginning of treatment).

Lastly, it is anticipated that to further evaluate the impact of resistance it will be necessary to include within the model subsequent retreatment and hospital admissions, and therefore the potential for those children colonised or infected with a resistant strain to have a higher probability of relapse and re-admission.

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 200 children at selected sites and frozen. The day 0 sample will be collected in the first 24 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 28 sample 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. Samples can be brought to the final follow-up visit, when they will be frozen and stored locally and then transferred on dry ice in batches to a central laboratory for processing and storage. Alternatively, 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 DETECTION OF RESPIRATORY BACTERIA AND VIRUSES IN BLOOD (SUB-STUDY)

EDTA blood samples (minimum volume 500µl) will be opportunistically obtained during routine phlebotomy from 50 children in the WARD group in whom a blood culture is also taken. The samples will be transferred to a central laboratory (Institute of Child Health, UCL) for processing and storage.

10.3 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.

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 (DPA number: Z5886415), 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 17141803.

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. NHS organisations 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 6.

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)

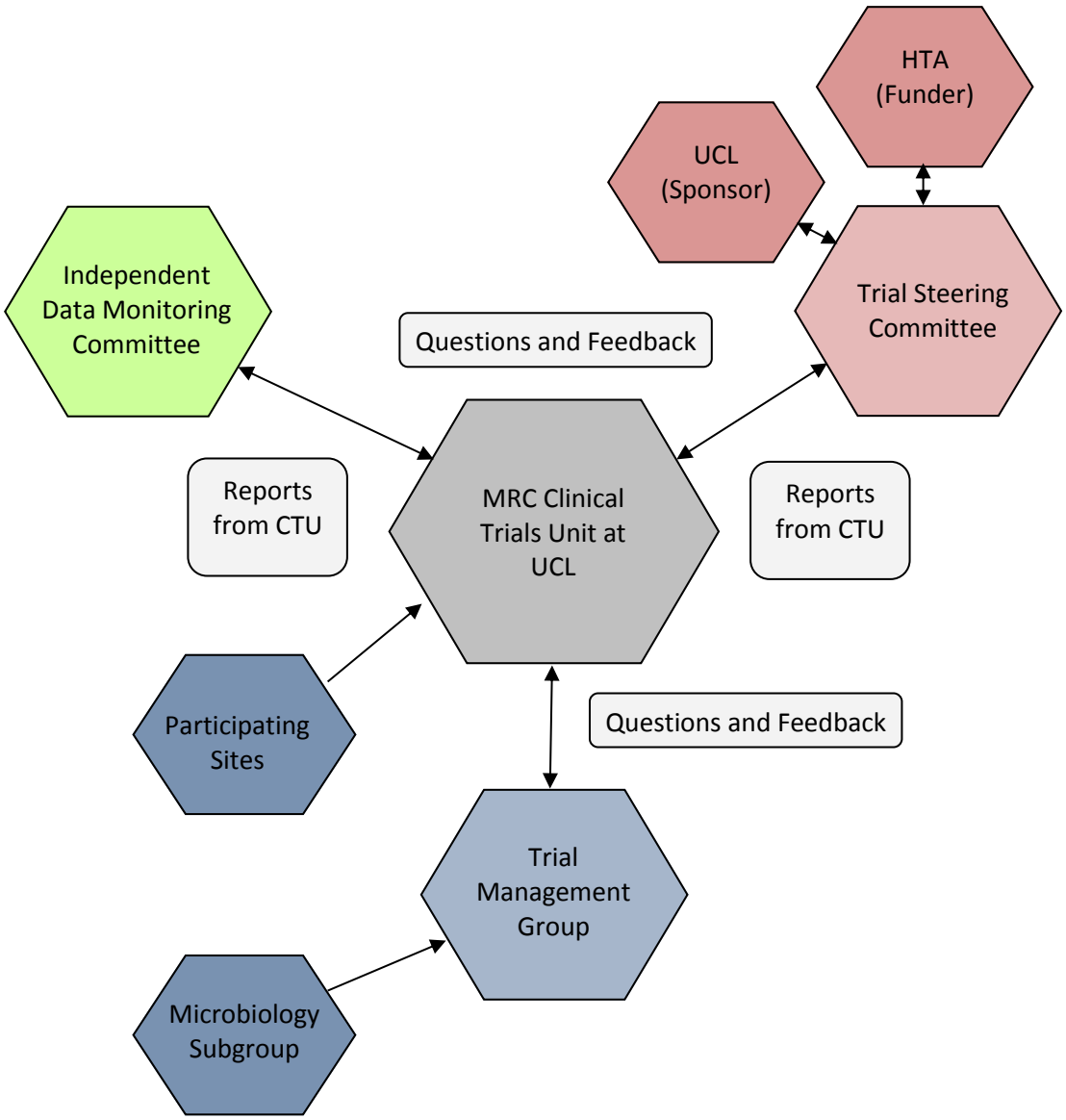
The Independent Data Monitoring Committee (IDMC) will be the only group which sees the confidential, accumulating data for the trial separately by randomised group. Reports to the IDMC will be produced by the trial statisticians. The frequency of meetings will be dictated in the IDMC charter. The IDMC 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 ROLE OF STUDY SPONSOR

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

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 3.0 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 "*Initial 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)

16.2 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.

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