Sponsor

Penta Child Health Research

Collaborating academic groups

St George's University of London

MRC Clinical Trials Unit

UCL

University of the Witwatersrand, Johannesburg

JCRC

University Teaching Hospital

AHRI Africa Health Research Institute

University of Cape Town

Funder

EDCTP

PediCAP

PediCAP

Impact of oral step-down to amoxicillin or co-amoxiclav and of duration of antibiotic therapy on effectiveness, safety and selection of antibiotic resistance in severe childhood community-acquired pneumonia (CAP): a randomised controlled trial

Version: **3.0**
Date: **05-November-2020**

MRC CTU at UCL ID: **PEDICAP**
ISRCTN #: **ISRCTN63115131**

Authorised by:

Name:	Professor Mike Sharland
Role:	Chief Investigator
Signature:	DocuSigned by: Michael Sharland 232789901B144D7...
Date:	05-Nov-2020
Name:	Professor Ann Sarah Walker
Role:	Trial Statistician
Signature:	DocuSigned by: 7289D1238A094E7...
Date	05-Nov-2020
Name:	Professor Elizabeth Molyneux
Role:	Chair of Trial Steering Committee
Signature:	DocuSigned by: Professor Elizabeth Molyneux EFD0548B39D14F8...
Date	05-Nov-2020
Name:	Laura Mangiarini
Role:	Chief Program Officer of Fondazione PENTA ONLUS
Signature:	DocuSigned by: Laura Mangiarini 6C75939B14D2477...
Date	05-Nov-2020

GENERAL INFORMATION

This document was constructed using the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL) Protocol Template Version 6.0. The CTU endorses the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative. It describes the PediCAP trial, coordinated by the MRC CTU at UCL, and provides information about procedures for entering children into it. The protocol should not be used as an aide-memoire or guide for the treatment of other children. 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 children for the first time are advised to contact the Infections Theme, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2013 (seventh revision), the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP), the principles of the UK Data Protection Act (no children will be recruited from the UK), the EU General Data Protection Regulation 2016/679 and applicable national regulations.

SPONSOR

Fondazione PENTA ONLUS is the trial Sponsor and has delegated responsibility for the overall management of the PediCAP trial to the MRC CTU at UCL.

FUNDING

This study is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) [RIA2017MC-2023]. MRC CTU at UCL is supported by the MRC (UK).

AUTHORISATIONS AND APPROVALS

This trial will be submitted for approval by Research Ethics Committees/Institutional Review Boards in each of the participating countries (South Africa, Uganda, Zambia, Zimbabwe) and the UK; and by all required regulatory authorities in each of the participating countries.

TRIAL REGISTRATION

This trial has been registered with the International Standard Randomised Clinical Trials Register, where it is identified as ISRCTN63115131.

SERIOUS ADVERSE EVENTS (SAE) AND OTHER NOTABLE EVENT REPORTING
Within 1 working day of becoming aware of an SAE/Other Notable Event, please email a completed SAE/Other Notable Event Form to the MRC CTU at UCL on mrcctu.pedicap@ucl.ac.uk

TRIAL SPONSOR

SPONSOR

Fondazione PENTA ONLUS Torre di Ricerca Pediatrica Corso Stati Uniti, 4 35127, Padova Italy		Switchboard: Fax:	+39 049 964 0122 +39 049 964 0123

FOUNDATION PENTA ONLUS STAFF

Chair:	Prof Carlo Giaquinto	Tel: Email:	+39 049 964 0122 carlo.giaquinto@unipd.it
Project Manager:	Francesca Viero	Tel: Email:	+39 049 821 5447 Francesca.viero@pentafoundation.org

TRIAL ADMINISTRATION

Please direct all queries to the PediCAP Trial Manager at MRC CTU at UCL in the first instance; clinical queries will be passed to the Medical Experts via the CTU Trial Manager.

NB: throughout this document, “MRC CTU at UCL” is generally abbreviated to “CTU”.

COORDINATING SITE

MRC Clinical Trials Unit at UCL Infections Theme 90 High Holborn London WC1V 6LJ United Kingdom		Switchboard: Fax: Email:	+44 20 7670 4700 +44 20 7670 4814 mrcctu.pedicap@ucl.ac.uk

MRC CTU STAFF AND AFFILIATES

Trial Statistician, Project Lead:	Prof Ann Sarah Walker, PhD MSc	Tel: Email:	+44 (0) 207 670 4726 rmjlasw@ucl.ac.uk
Physician, co-investigator:	Prof Diana M Gibb, MD MSc	Tel:	+44 (0) 207 670 4905

		Email:	diana.gibb@ucl.ac.uk
Clinical Project Manager, co-investigator:	Ben Spittle	Tel: Email:	+44 (0) 207 670 4691 mrcctu.pedicap@ucl.ac.uk
Statistician:	Dr Michelle Clements, PhD	Tel: Email:	+44 (0) 207 670 4912 michelle.clements@ucl.ac.uk
Trial Manager:	Emily Dennis	Tel: Email:	+44 (0) 207 670 4660 mrcctu.pedicap@ucl.ac.uk
Data Manager:	Nishda Naufal, BSc	Tel: Email:	+44 (0) 207 670 4907 mrcctu.pedicap@ucl.ac.uk
Policy Coordinator:	Annabelle South	Tel: Email:	+44 (0) 20 7670 4827 a.south@ucl.ac.uk

SGUL

St George's University of London
Cranmer Terrace, Tooting,
London SW17 0RE
United Kingdom

Chief Investigator:	Prof Mike Sharland, MD MSc	Tel: Email:	+44 (0) 20 8725 0666 msharland@sgul.ac.uk
Co-investigator, Trial Physician:	Dr Julia Bielicki, MRCPCH	Tel: Email:	+44 (0) 208 725 5382 jbielick@sgul.ac.uk

RECRUITING SITE STAFF

SOUTH AFRICA: Country Co-Principal Investigators Prof Shabir Madhi and Prof Nigel Klein

Lead Site:
Chris Hani Baragwanath Academic Hospital, Soweto, Gauteng Province
Wits Health Consortium
31 Princess of Wales Terrace
Parktown
Johannesburg
South Africa

Co-Principal Investigator:	Prof Shabir Madhi, MBBCh PhD	Tel: Email:	+27 11 983 4283 madhis@rmpru.co.za
Trial Physician	Dr David Moore, MBBCh PhD	Tel: Email	+27 83 297 2468 david.moore@wits.ac.za
Trial Physician	Prof Ziyaad Dangor, MBBCh, PhD	Tel: Email	+27 83 471 0933 Ziyaad.dangor@wits.ac.za

Trial Manager:	TBA	Tel: Email:	

Other Site:
Africa Health Research Institute (AHRI)
King Edward VIII Hospital, Sydney Road
Umbilo, Durban 4013
South Africa

Co-Principal Investigator:	Prof Nigel Klein, MBChB Phd	Email:	n.klein@ucl.ac.uk
Co-Principal Investigator:	Dr Moherndran Archary	Email:	archary@ukzn.ac.za
Trial Manager:	Anne Derache, PhD	Tel: Email:	+27 78 396 4641 anne.derache@ahri.org

UGANDA: Country Principal Investigator Dr Victor Musiime

Lead Site:
Makerere University, College of Health Sciences
P. O. Box 7072
Kampala, Uganda

Principal Investigator:	Dr Victor Musiime, MBChB, MMed, PhD	Tel: Email:	+ 256 414 699134 vmusiime@jcrc.org.ug
Co – Principal Investigator:	Prof Philippa Musoke, MBChB, PhD	Email:	pmusoke@mujhu.org
Trial Manager:	Dr Damalie Nalwanga, MBChB, MMED	Email:	damalielwanga@gmail.com

ZAMBIA: Country Principal Investigator Dr Veronica Mulenga

Lead Site:
University of Zambia/School of Medicine
University Teaching Hospitals- Children Hospital
PO Box 50110
Lusaka Zambia

Principal investigator:	Dr Veronica Mulenga MBChB, MSC, Dip Epidemiology	Tel: Email:	+26 0211 251680 veromulenga@gmail.com
Co-Principal Investigator:	Dr Chishala Chabala, MBChB, MMed, MSc	Tel: Email:	+260 977 849 cchabala@gmail.com
Trial Manager:	Jacqueline Hangoma Kaira	Email:	jhangomakaira@gmail.com

ZIMBABWE: Country Co-Principal Investigators Prof Hilda Mujuru, Prof Kusum Nathoo and Prof Mutsa Bwakura-Dangarembizi

Lead Site:
University of Zimbabwe Clinical Research Centre (UZCRC)
P.O.Box A, 1578 Avondale
Harare, Zimbabwe

Co-Principal Investigator:	Dr Hilda Angela Mujuru, MBChB MMed (Paeds), MSc	Email:	hmujuru@mweb.co.zw
Co-Principal Investigator:	Prof Kusum Nathoo, MBChB, DCH, MRCP, MSc	Tel: Email:	+ 263 242 791 631 ext 2224 knathoo@mweb.co.zw
Co-Principal Investigator:	Prof Mutsa Bwakura-Dangarembizi MMed (Paeds), MSc	Tel: Email:	+ 263 772 601 735 dangas@zol.co.zw knathoo@mweb.co.zw
Trial Manager:	Ennie Chidziva	Tel: Email:	+263 242 701 717 echidziva@uzcrc.org

OTHER RESPONSIBLE INDIVIDUALS

PHARMACOLOGY

University of Cape Town
K-45 Old Main Building
Groote Schuur Hospital,
Observatory 7925
Cape Town,
South Africa

Co-investigator:	Prof Paolo Denti, PhD	Tel: Email:	+27 21 404 7719 paolo.denti@uct.ac.za
Co-investigator:	Prof Helen McIlleron, PhD	Tel: Email:	+27 214 066292 Helen.mcilleron@uct.ac.za

Analytical Services International Ltd (ASI)
St. George's University of London
Cranmer Terrace
London
SW17 0RE

Co-investigator:	Stewart Hollington	Tel: Email:	+44 (0) 20 8725 2845 stewart.hollington@bioanalytics.co.uk
Co-investigator:	Dr Joe Standing, PhD	Tel: Email:	+ 44 207 905 2370 j.standing@ucl.ac.uk

MICROBIOLOGY

Campus Drie Eiken,
Universiteitsplein 1
D.S.623
2610 Wilrijk
Belgium

Co-investigator:	Prof Surbhi Malhotra-Kumar, PhD	Tel:	+32 3 265 27 52
		Email:	surbhi.malhotra@uantwerpen.be
Co-investigator:	Dr Tomislav Kostyanev, PhD	Tel:	+32 3 265 25 50
		Email:	Tomislav.Kostyanev@uantwerpen.be

HEALTH ECONOMICS

Health Economics Unit
School of Public Health and Family Medicine
University of Cape Town

Co-investigator:	Professor Susan Cleary, PhD	Tel:	+27214066755
		Email:	Susan.Cleary@uct.ac.za
Co-investigator:	Lucy Cunnama, MPH	Tel:	+27214066754
		Email:	Lucy.Cunnama@uct.ac.za

Health Systems and Household Economics Research Unit
the Swiss Tropical and Public Health Institute
Basel
Switzerland

Co-investigator:	Prof Günther Funk, PhD	Tel:	+41612848354
		Email:	guenther.fink@swisstph.ch
Co-investigator:	Gillian Levine, PhD, MPH	Tel:	+41612848732
		Email:	gillian.levine@swisstph.ch

GLOBAL HEALTH NETWORK

Centre for Tropical Medicine and Global Health
Nuffield Department of Medicine Research Building,
University of Oxford, Old Road Campus,
Roosevelt Drive, Headington,
Oxford OX3 7FZ, UK

Co-investigator:	Prof Trudie Lang, DPhil	Tel:	+44 1865 612 90
		Email:	trudie.lang@ndm.ox.ac.uk

LAY SUMMARY

This study is designed to work out the best way to treat children aged 2 months to 6 years of age, who weigh between 3kg and 30kg, and who have pneumonia (chest infection) that has developed while they are at home and is so serious that they need to be treated in hospital. The study will run in South Africa, Uganda, Zambia and Zimbabwe.

These children often receive antibiotics by injection for a long time. The children have to stay in hospital for these injections, which is difficult for parents/carers and expensive. Being in hospital means the children may pick up other infections, too, including new infections which cannot be treated by standard antibiotics. These are called “antibiotic resistant” infections.

Some doctors change the children onto antibiotics that can be taken by mouth (called “oral” antibiotics) as soon as they are well enough. Oral antibiotics should be as good as continuing with injections of antibiotics for these children.

No studies have specifically looked at this in this group of children who are in hospital with serious chest infections in low and middle-income settings. This means we cannot formally recommend changing to oral antibiotics once children are well enough.

Finally, there is no evidence for how long children with serious chest infections actually need to be on antibiotics. The longer people take antibiotics, the more likely it is that the other bacteria that we all live with us (and not the ones making us sick!) will become more resistant to antibiotics. This would mean that antibiotics won’t work as well for infections in the future.

So, we want to give children just enough antibiotics to make them well now, but not so many antibiotics that bacteria develop more resistance and the antibiotics perhaps won’t work next time.

Surprisingly almost no studies have looked at exactly how long children with serious chest infections need to take antibiotics to get better.

In this study, all children will start on the World Health Organisation (WHO)-recommended injectable antibiotics. When they are well enough to take drugs by mouth, they will be to move to one oral antibiotic called co-amoxiclav, or another oral antibiotic called amoxicillin, or they will stay on injectable antibiotics. This would be decided by chance (“randomisation”).

Both of these oral drugs should be highly effective, but we want to find out if co-amoxiclav is actually any better.

Co-amoxiclav is mostly given to children as a liquid, and needs to be kept cool. In the trial we will use tablets that become liquid when mixed with small amounts of other liquids (e.g. water) instead. If co-amoxiclav really is better, we need to make sure that these tablet formulations become more widely available.

We also don’t know how long the antibiotic treatment needs to last. Children will be randomised to get their antibiotics for 4, 5, 6, 7 or 8 days in total. These durations are used in different parts of the world and there is no evidence that any one is better than the other.

We will follow children for 28 days over the telephone and through face to face visits to find out whether they have had any problems. We will focus on whether they have to be admitted to

hospital again or whether they have died. We will also look at how long they have to stay in hospital (since parents/carers typically have to pay for this), how many antibiotics children take during the month after being admitted to hospital, how much they need other treatments like extra oxygen, and how much all their care costs.

In an extra part of the study, we will look at amount of two drugs that make co-amoxiclav. Across the world, different ratios are used and there are no data to tell us which might be the best for children. In the main part of the study, we will use a tablet with 7 parts amoxicillin to 1 part clavulanate, because this is most commonly used in Europe. In a subset of these children, we will measure how much of the drug gets into their blood. In the extra part of the study, we will measure drug levels in children getting either 4 parts amoxicillin to 1 part clavulanate or 14 parts amoxicillin to 1 part clavulanate. These ratios are each used elsewhere in the world. We will also look to see whether these ratios lead to different rates of side-effects like tummy upsets which are important for parents.

So, in this one study, we aim to answer all of the following questions to work out the best way to treat children aged 2 months to 6 years who have chest infections that have developed at home and are so serious that they need to be treated in hospital:

1. Is the rate of clinical cure better if children move from injectable antibiotics to oral co-amoxiclav or oral amoxicillin antibiotics once they are well enough to take drugs by mouth, and how does this compare to staying on injectable antibiotics?

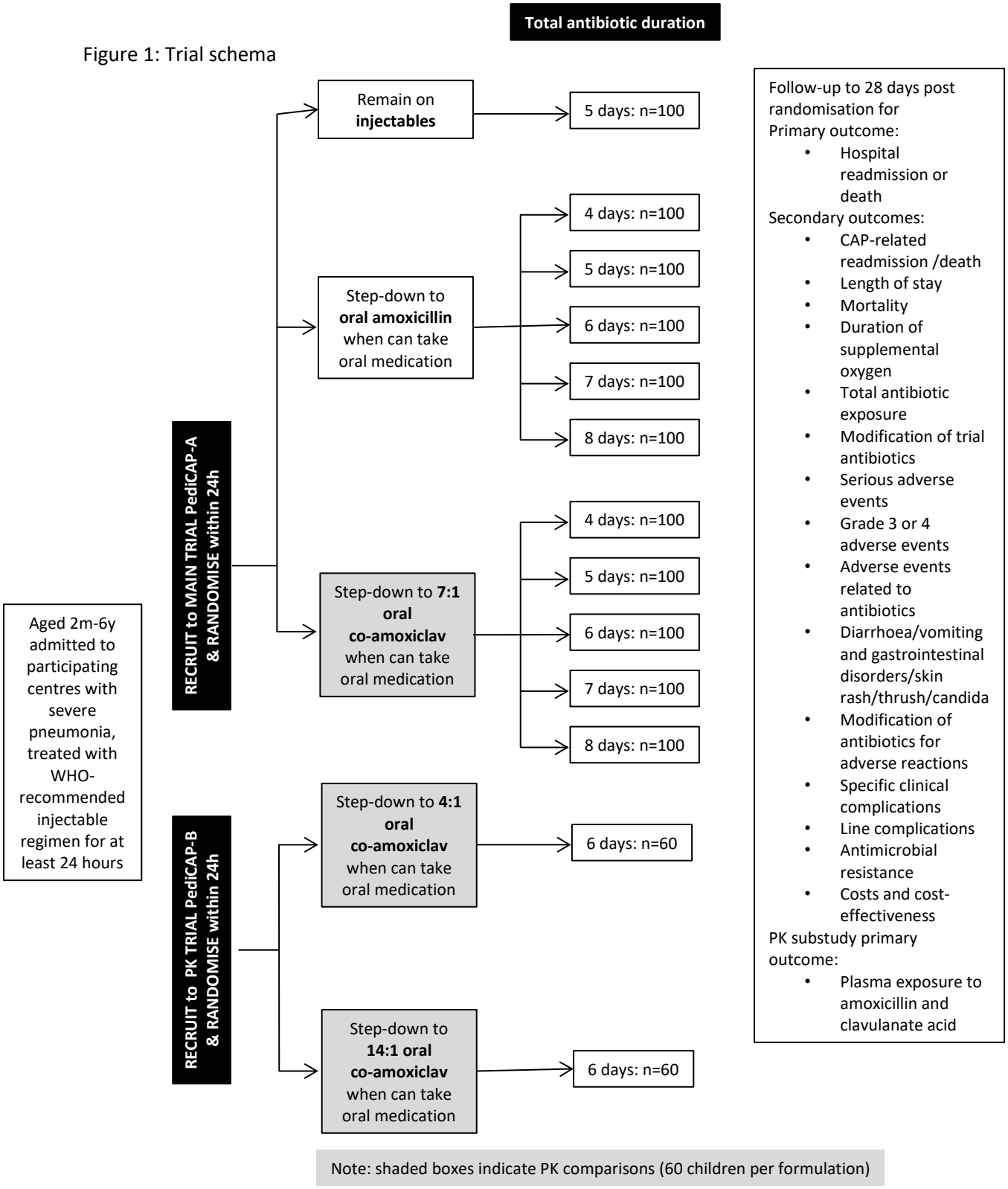
2. What is the best duration of antibiotic treatment for children that gives good rates of clinical cure while reducing how long they have to stay in hospital, the side effects they experience and the presence of other antibiotic-resistant bacteria?

3. Does this best duration depend on other factors, such as age, having been exposed to HIV, having malnutrition or how serious the chest infection is, suggesting that how long children get antibiotics for should be vary based on these risk factors?

4. What ratio of amoxicillin to clavulanate should be used in co-amoxiclav for children?

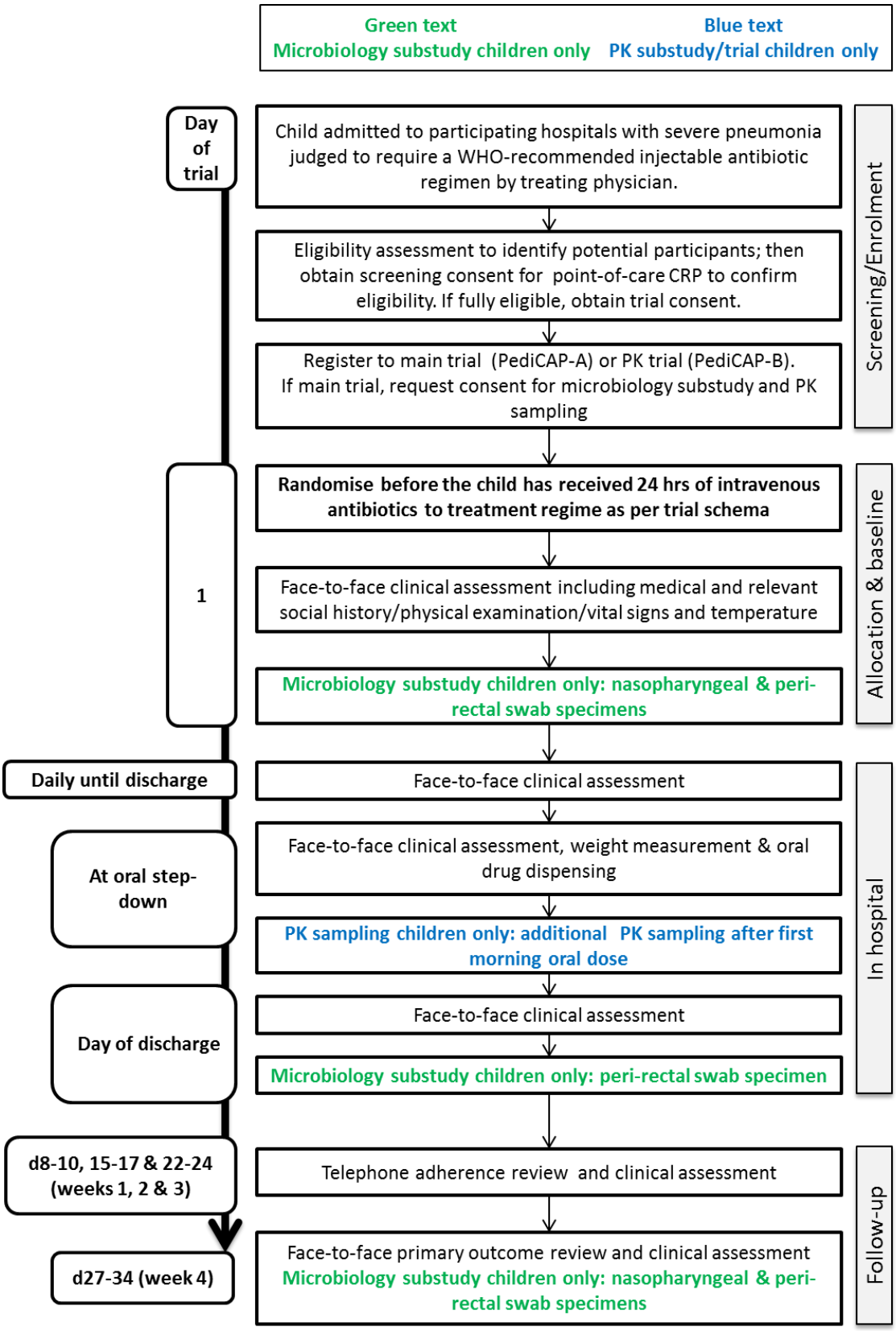
TRIAL SCHEMA

Figure 1: Trial schema



Note: each child would be approached for recruitment into either PediCAP-A or PediCAP-B with the PediCAP-A/PediCAP-B specific patient information sheet. All children in PediCAP-B would undergo PK sampling (consent required for enrolment into PediCAP-B). Only 60 of the 500 children randomised to co-amoxiclav 7:1 in PediCAP-A would undergo PK sampling (additional consent will be sought for this before randomisation in PediCAP-A).

Figure 2: Trial Entry, Randomisation and Treatment



Note: children in the microbiology substudy will have three peri-rectal (baseline, discharge and d28) and two nasopharyngeal (baseline and one of discharge/d28) swabs specimens taken, with the timing of the second nasopharyngeal sample being determined by randomisation.

SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Short title	PediCAP (Paediatric Community Acquired Pneumonia)
Long Title of Trial	Impact of oral step-down to amoxicillin or co-amoxiclav and of duration of antibiotic therapy on effectiveness, safety and selection of antibiotic resistance in severe childhood community-acquired pneumonia (CAP): a randomised controlled trial
Version	3.0
Date	05 November 2020
ISRCTN #	ISRCTN6311513163115131
Study Design	An open-label, parallel group, 2x5 factorial randomised trial assessing 2 different oral step-down antibiotics (amoxicillin and co-amoxiclav (amoxicillin:clavulanate 7:1)) given after intravenous antibiotics for a total of 5 different durations (factorial design) with an additional continued intravenous control group, using a novel design to optimise duration of treatment (main trial, PediCAP-A) Plus a parallel Phase II pharmacokinetic (PK) trial comparing two additional different ratios for one of the oral step-down options, co-amoxiclav (14:1 and 4:1) (PediCAP-B), to enable the PK of all three ratios to be compared across the main trial (PediCAP-A) and the PK trial (PediCAP-B) Each child would be approached for recruitment into either PediCAP-A or PediCAP-B.
Setting	Hospitals in South Africa, Uganda, Zambia and Zimbabwe.
Type of Participants to be Studied	Children aged 2 months to 6 years inclusive and weighing >=3kg and <30kg hospitalised with severe community acquired pneumonia and with C-reactive protein >10 mg/l on a semi-quantitative point-of-care test at screening, who are about to start or who have started intravenous antibiotics for severe CAP
Interventions to be Compared	All children will initiate or have already initiated treatment with WHO-recommended intravenous antibiotics. In the main trial (PediCAP-A), children who have received at most 24h of intravenous antibiotics will be randomised to step-down from intravenous antibiotics when they are clinically stable and able to take oral medication to: ▪ either oral amoxicillin or oral co-amoxiclav (7:1 amoxicillin:clavulanate) (1:1), both as dispersible tablets ▪ for a total duration of 4, 5, 6, 7 or 8 days antibiotics (1:1:1:1:1) (from start of intravenous antibiotics); (total 10 groups) ▪ or to remain on intravenous antibiotics for a total of 5 days following current WHO recommendation (additional eleventh group of the same size as each duration/drug group). In the parallel Phase II PK trial (PediCAP-B), children who have received at most 24h of intravenous antibiotics will be randomised to step-down from intravenous antibiotics when they are clinically stable and able to take oral medication to

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	▪ either oral co-amoxiclav 4:1 or 14:1 (1:1) for a total duration of 6 days antibiotics (from start of intravenous antibiotics) (two groups) All children will receive at least 24h of intravenous antibiotics before stepping down to oral medication.
Study Hypothesis	PediCAP-A ▪ Oral co-amoxiclav step-down is superior to oral amoxicillin step-down for preventing readmission or death within 28 days of commencing treatment. ▪ Randomising children between 5 different total durations of antibiotics including intravenous plus oral step-down will identify the minimum duration providing outcome rates within specific thresholds of the WHO-recommended 5 days' intravenous regimen. PediCAP-A plus PediCAP-B ▪ Clavulanate PK exposures will be linear across the three formulation strengths used worldwide (4:1, 7:1, 14:1)
Primary Outcome Measure(s)	For the main trial (PediCAP-A): ▪ Hospital readmission or death within 28 days of randomisation (all-cause) For the Phase II PK trial (PediCAP-B): ▪ Plasma exposure to amoxicillin and clavulanate
Secondary Outcome Measure(s)	For the main trial (PediCAP-A), within 28 days of randomisation: ▪ CAP-related readmission or CAP-related mortality ▪ Length of stay required during the index hospitalisation, and overall through 28 days ▪ Mortality (all-cause) ▪ Duration of supplemental oxygen during the index hospitalisation ▪ Total days of antibiotic exposure through 28 days ▪ Modification of randomised antibiotics for any reason except early stopping or receipt of subsequent course of antibiotics for any reason ▪ Modification of randomised antibiotics for inadequate response or additional courses for CAP relapse ▪ Serious adverse events ▪ Grade 3 or 4 adverse events ▪ Adverse events of any grade related to antibiotics ▪ Key solicited events, specifically diarrhoea, vomiting and gastrointestinal disorders, skin rash, thrush/candida ▪ Modification of antibiotics for adverse reactions ▪ Specific clinical complications, including sepsis, lung abscess, empyema ▪ Line complications ▪ Antimicrobial resistance (see Substudies below) ▪ Cost and cost-effectiveness (see Substudies below)
Randomisation	In the main trial (PediCAP-A), children will be allocated 1:1 to the different step-down options (amoxicillin or co-amoxiclav in 7:1 ratio) and 1:1:1:1:1 to the different total duration of antibiotic therapy using a factorial design, or to continue on intravenous antibiotics (11 groups in total) In the Phase II PK trial (PediCAP-B), children will be allocated 1:1 to co-amoxiclav in either 4:1 or 14:1 ratios
Number of Participants to be Studied	1100 in the main trial (PediCAP-A) (100 per randomised group) 120 in the Phase II PK trial (PediCAP-B) (60 per formulation)

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Duration	Each child will be followed for 28 days from randomisation. The trial will recruit over 23 months (total 2 year duration)
Substudies	Pharmacokinetics (PK): evaluating and modelling the PK of amoxicillin and co-amoxiclav in three different ratios (7:1 in the main trial (PediCAP-A), plus 4:1 and 14:1 in the parallel PK trial (PediCAP-B) when administered orally as step-down treatment in severe CAP. 60 of 500 children randomised to co-amoxiclav 7:1 in PediCAP-A would undergo PK. All 120 children randomised to co-amoxiclav 4:1 vs 14:1 would undergo PK. Microbial sampling: investigating changes in nasopharyngeal and faecal prevalence of antimicrobial resistance in relation to randomisation to amoxicillin/co-amoxiclav, duration of antibiotic exposure and inpatient stay. Health economics and equity: assessing the costs and cost-effectiveness of different treatment strategies in the randomised trial as well as their equity impacts at household level
Funder	European Developing Countries Clinical Trials Partnership (EDCTP)
Sponsor	Fondazione PENTA ONLUS
Chief Investigator	Professor Mike Sharland

TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

ASSESSMENTS (PediCAP-A and PediCAP-B) Face-to-face (f2f) ■ Face-to-face (f2f) or telephone □	DAYS IN TRIAL (d)									
	Screening d-1 to d1	Randomisation d1	Daily until discharge	Oral step-down	At discharge	Week 1 d8-10	Week 2 d15-17	Week 3 d22-24	Week 4 d27-34	Any acute event
Trial participation										
Parent/Carer information sheet	X	X								
Informed consent	X	X								
Drug supply dispensing				X†						
Adherence and tolerability[a]					X	X				
Clinical assessment										
Baseline data collection[b]		X								
Weight		X		X					X	
Vital signs[c]		X	X		X					X[d]
Symptoms and clinical signs[e]		X	X		X	X	X	X	X	X[d]
Concomitant care/healthcare utilisation[f]			X		X	X	X	X	X	X[d]
Laboratory assessment										
Point of care C-Reactive Protein[g]	X									
Haematology[h]		(X)	(X)			(X)	(X)	(X)	(X)	(X)
Biochemistry[i]		(X)	(X)			(X)	(X)	(X)	(X)	(X)
Microbiological investigations[j]		(X)	(X)			(X)	(X)	(X)	(X)	(X)
Radiological assessment										
Chest X-ray[k]		(X)	(X)							(X)
PK substudy: additional tests										
Pharmacokinetics samples[l] (total 10ml)				X						
Microbiology substudy: additional tests										
Peri-rectal swab[m]		X			X				X	
Nasopharyngeal swab[n]		X			[X][n]				[X][n]	

X† indicates that oral step-down antibiotics will be prescribed to complete the randomised total duration of antibiotic therapy at the point the child can tolerate oral medication

(X) indicates tests that may be done if the child's condition requires it or allows it and is local standard of care, but these investigations are not mandatory and are not paid for by the trial. Results will be collected, if available.

Note: Week 4 visit may be conducted by telephone if child is unable to come to clinic. For any child in hospital on day 28, the total duration of that hospitalisation and resource use during it will be collected through to discharge.

Additional explanatory notes for investigations

[a] Nurse administered questionnaire at discharge and telephone follow-up.

[b] Includes sociodemographic and socioeconomic information, mode of delivery, documentation of immunisation status (including taking copies of immunisation records where available (copies will be taken at week 4 if not brought at the original admission)), documentation of any underlying diseases, duration of symptoms to date, recent antibiotic exposure, height/length and upper middle arm circumference. Height/length and upper middle arm circumference may be collected post-baseline if not possible to assess at trial entry.

[c] Includes vital parameters (respiratory and heart rate and oxygen saturation) and temperature.

[d] If clinically reviewed by the trial team.

[e] Includes documentation of relevant physical signs and symptoms, as well as specific solicited side-effects and adverse events post-randomisation.

[f] For example administration of parenteral fluids and antibiotics, intensive care transfers and discharge from hospital as well as re-hospitalisation during the follow-up period, and further antibiotic treatment post-discharge; for outpatients elicited during phone follow-up.

[g] Semi-quantitative point-of-care test using finger or heel prick only, or venous blood taken as part of routine care.

[h] If available (performed locally following standard of care; not to be done specifically for research), haemoglobin, platelet count, leukocyte count, neutrophil count, white cell count, eosinophil count.

[i] If available (performed locally following standard of care; not to be done specifically for research), C-reactive protein, procalcitonin, urea, creatinine and electrolytes.

[j] If available (performed locally following standard of care; not to be done specifically for research), any relevant bacteriology results as well as any virology, for example rapid testing for RSV and Influenza A/B (any method) performed locally.

[k] Results of any chest X-rays as reported at local site by radiology staff will be recorded; digital copies of the X-rays will be collected wherever possible.

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

[l] Co-amoxiclav pharmacokinetics: up to 5 PK samples (2ml per sample) after the first oral dose taken in the morning (n=60 in the main trial (PediCAP-A), all 120 children in the Phase II PK trial (PediCAP-B))

[m] Peri-rectal swab (or whole stool if passed or available from a nappy) at trial entry, discharge, and at d28 follow-up (n=330 in the main trial (PediCAP-A), 66 per site).

[n] A nasopharyngeal swab at trial entry, and at either discharge or d28 follow-up (i.e. two swabs per child) (same 330 children as peri-rectal swabs). The second swab being at discharge vs day 28 will be determined by randomisation to ensure comparability.

CONTENTS

ABBREVIATIONS

Abbreviation	Expansion
AE	Adverse event
AR	Adverse reaction
AUC	Area under the curve
BD	Bis in die (give twice a day)
BNFC	British National Formulary for Children
CAG	Community advisory group
CAP	Community acquired pneumonia
CET	Cost-effectiveness threshold
CF	Consent Form
CI	Chief Investigator
CI	Confidence interval
CPM	Clinical Project Manager
CRF	Case Report Form
CRP	C-reactive protein
CTU	See MRC CTU at UCL
DAIDS	Division of AIDS
D or d	Day
DALY	Disability adjusted life year
DMC	Data Monitoring Committee
DMP	Data management plan
DNA	Deoxyribonucleic acid
EDCTP	European and Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
EML	Essential Medicines List
ERC	Endpoint Review Committee
ESBL	Extended Spectrum Beta-Lactamases
EU	European Union
FDA	(US) Food and Drug Administration
GAPP	Global action plan for the prevention of pneumonia
GCP	Good Clinical Practice
h	Hours
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICER	Incremental Cost Effectiveness Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IMP	Investigational medicinal product

Abbreviation	Expansion
IQR	Interquartile range
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
IV	Intravenous
LMIC	Low- and middle-income countries
MDR-GNB	Multi-drug resistant gram-negative bacteria
MIC	Median Inhibitory Concentration
MOP	Manual of Operations
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to "CTU")
MRSA	Methicillin resistant Staphylococcus aureus
MSSA	Methicillin susceptible Staphylococcus aureus
MUAC	Middle-upper arm circumference
NA	Not applicable
NCDC	National Center for Disease Control
NIMP	Non-investigational-medicinal product
PD	Pharmacodynamics
PediCAP	Paediatric Community Acquired Pneumonia
PENTA	Fondazione PENTA ONLUS
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PMC	PubMed Central
QA	Quality Assurance
QC	Quality Control
QMAG	Quality Management Advisory Group
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGC	Research Governance Committee
RSA	Republic of South Africa
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

Abbreviation	Expansion
SSA	Site-specific approval
SSG	Scientific Strategy Group
SUSAR	Suspected unexpected serious adverse reaction
T	Time
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UK	United Kingdom
UNICEF	United Nations children's fund
YLD	Years of life lived with disability
YLL	Years of life lost
WHO	World Health Organisation

1 BACKGROUND

1.1 THE ADVERSE IMPACT OF SEVERE PNEUMONIA ON CHILD HEALTH IN AFRICA

Community-acquired pneumonia (CAP) is common and remains associated with substantial morbidity and mortality, especially in lower and middle-income countries (LMIC) [1]. In 2016, 1 per 1000 children younger than 5 years of age was estimated to die due to pneumonia globally [2, 3]. In Africa, pneumonia incidence is estimated at one episode per 3 child-years in young children and severe pneumonia has a mortality of 10-15% [1, 4, 5]. While the proportion of childhood deaths attributable to pneumonia decreased in the 1990s, this has since remained at 18% [6]. Many children with pneumonia in LMIC require inpatient management. In Malawi, 36% of 1-5 year-olds presenting with pneumonia were admitted to hospital and a quarter of these suffered from very severe pneumonia (according to pre-2012 World Health Organisation (WHO) definitions) [5]. In Papua New Guinea the mortality of severe pneumonia requiring hospitalisation was 6%, but another 7% were readmitted with severe pneumonia within 1 month of discharge [7]. In Zambia, the mortality of severe pneumonia managed in hospital was recently estimated at 18% [8]. An overall 5% out-of-hospital mortality has been reported for children discharged in Uganda after inpatient management of an infection, with children of mothers with a lower level of education at much higher risk of death after discharge [9].

The UNICEF and WHO Global Action Plan for prevention and control of pneumonia (GAPP) data [10], indicates that care-seeking of under-fives with pneumonia symptoms in countries represented in PediCAP is relatively high (South Africa 88%, Uganda 80%, Zambia 70%, Zimbabwe 59%). In 2015, high mortality rates from pneumonia were still observed despite improvements since the early 2000s (South Africa 7/1000 live births, Uganda 8.6/1000, Zambia 9.8/1000, and Zimbabwe 10.2/1000) [2]. Correspondingly, acute respiratory infections account for 17% of under-five deaths in South Africa, 16% in Uganda, 14% in Zambia and 15% in Zimbabwe [2]. No robust data are available comparing hospitalisation rates and outcomes across African countries.

The costs associated with inpatient care for severe childhood pneumonia in LMIC are themselves substantial, estimated at up to US$600 per episode [7]. An early intravenous to oral switch of antibiotics is known to reduce episode costs by around 40% in high-income settings [11], without compromising efficacy.

1.2 THE ROLE OF OPTIMAL ANTIBIOTIC TREATMENT IN MANAGING SEVERE PNEUMONIA

While standardising care is one important component in reducing mortality from severe pneumonia initially requiring hospitalisation, the antibiotics used are also clearly key. Optimising antibiotic treatment includes defining the right drug (for the indication), right duration, right delivery (route of administration) and right dose. At present, strong data to support clinical decision-making for each of these factors in severe childhood pneumonia requiring inpatient care in LMIC are lacking.

1.2.1 RIGHT DRUG

The selection of antibiotics in bacterial infections should be guided by knowledge of the microbiological epidemiology of the disease in the region of interest with subsequent adaptation according to the causative bacteria identified. However, determining specific causative pathogens in childhood pneumonia is challenging, particularly during routine care. In research studies, bacterial pneumonia is still common among children hospitalised with pneumonia in LMICs [12]. *Streptococcus pneumoniae* remains the most frequently isolated bacterial pathogen, suggesting that

a penicillin or aminopenicillin-based regimen should be appropriate. However, concerns are emerging about other bacteria causing severe pneumonia, especially *Staphylococcus aureus* but also *Haemophilus influenzae*, in pneumococcal-vaccinated LMIC populations [12-14]. Production of beta-lactamases by these bacteria can be overcome by use of antibiotic combinations and/or co-formulations of beta-lactams, such as amoxicillin, with beta-lactamase inhibitors, such as clavulanate as co-amoxiclav. Reconstituted co-amoxiclav suspension requires refrigeration [15] which is not always available in LMIC settings and newer dispersible tablets avoid issues with cold storage. Additionally, co-amoxiclav is available, and used in children across the world, in various different ratios of amoxicillin:clavulanate, namely 4:1, 7:1 and 14:1. There are virtually no data in children to inform what might be the most appropriate ratio for use in this indication, whether clavulanate is saturable (i.e. concentrations increase linearly with dose or reach a threshold), and whether different ratios are associated with different rates of side-effects such as diarrhoea.

1.2.2 RIGHT DURATION

In a randomised controlled trial (RCT) comparing two antibiotic regimens for inpatient treatment of severe pneumonia conducted in Papua New Guinea, children received the intravenous comparators for 5 days but were treated with additional oral antibiotics to complete a total treatment duration of 14 days [7]. In a similar multinational multicentre trial, the overall duration of antibiotic was 5 days intravenous plus 5 days oral treatment. A 2017 Cochrane review noted that there were no RCTs comparing a shorter to longer course of intravenous antibiotics (with or without oral antibiotics) in severe childhood pneumonia [16, 17]. However, short oral antibiotic courses of only 3 days have been recommended for non-severe childhood pneumonia in LMIC settings [17], and in hospitalised adults 3-5 days antibiotic treatment is non-inferior to 8-10 days [18, 19].

1.2.3 RIGHT DELIVERY

Evidence from previous RCTs conducted in Pakistan involving young children with severe pneumonia not requiring inpatient care support the use of oral antibiotics [20, 21]. Another LMIC multinational multicentre open-label trial compared children with severe pneumonia randomised to either 48 hours of inpatient injectable penicillin or inpatient oral amoxicillin, followed by a further 5 day course of amoxicillin at home [22]. It found that injectable penicillin and oral amoxicillin were equivalent, with potential benefits of oral treatment including decreases in risk of needle-borne infections, need for referral or admission, administration costs and costs to the family. However, these trials excluded children with very severe pneumonia and persistent vomiting; and in one [21], it was noted that children with certain baseline characteristics were more likely to be assigned to the initial injectable group which included a period of inpatient care.

1.2.4 RIGHT DOSE

Dosing is influenced by the type of antibiotic being considered (e.g. beta-lactam), as this determines the relevant pharmacokinetic/pharmacodynamic (PK/PD) target. In addition, knowledge of prevalent antibiotic resistance in key pathogens, such as pneumococcus, can be important. The key PK/PD parameter for beta-lactams (including amoxicillin) is time spent above the minimal inhibitory concentration (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 [23]. Although early data suggested that twice daily dosing would achieve required T>MIC for total daily amoxicillin doses of 25-50mg/kg [24], higher daily doses have been recommended when amoxicillin is administered in a twice daily regimen to treat pneumonia [25]. This is likely to be particularly relevant in sub-Saharan Africa, where high levels of antimicrobial resistance, including pneumococcal penicillin resistance of around 20% in children with pneumonia, have been observed [26].

1.3 CURRENT WHO RECOMMENDATIONS

Current WHO recommendations for treating severe pneumonia in hospital are summarised in **Table 2** below and suggest these children should be treated with injectable antibiotics for at least 5 days. One main advantage of injectable regimens is that they cover a greater spectrum of pathogens, with gentamicin having activity against methicillin susceptible *Staphylococcus aureus* (MSSA) and respiratory Gram-negative bacteria, compared to oral amoxicillin alone which is recommended by WHO for non-severe pneumonia. WHO guidelines therefore currently recommend that children requiring treatment with broader-spectrum intravenous regimens remain hospitalised for the minimal duration of administration [27, 28]. The WHO recommendations were made in 2013-2014; local standard of care may differ from WHO recommendations, taking into account any local susceptibility patterns. Such intravenous regimens have previously been investigated in several trials. Managing severe pneumonia is therefore associated with prolonged hospital stays, high healthcare and societal costs [29], and carries a significantly increased risk of nosocomial infections or acquisition of multidrug-resistant colonising bacteria during hospitalisation.

Table 2: 2013-2014 WHO recommendations for antibiotic treatment in childhood pneumonia

DEFINITION	DRUG	DOSE	DELIVERY (ROUTE)	DURATION	COMMENT
Revised WHO classification and treatment of pneumonia in children at health facilities (2014)[30]					
Fast breathing and/or chest indrawing pneumonia	Amoxicillin	Approx 80mg/kg/d in 2 doses	Oral	5d	High HIV prevalence
				3d	Fast-breathing and low HIV prevalence
	Failure to improve → referral to hospital				
Severe pneumonia	Ampicillin or Benzylpenicillin	50mg/kg every 6 hours 50,000 IU/kg every 6 hours	Intramuscular/ intravenous	At least 5d	Ceftriaxone may be used as second-line treatment
	Gentamicin	7.5mg/kg once a day			
Pocket book of hospital care for children, 2nd edition (2013)[27]					
Pneumonia	As above for non-severe pneumonia				
Severe pneumonia	As above for severe pneumonia				
Severe pneumonia failing to improve and staphylococcal pneumonia suspected	Switch penicillin to cloxacillin	50mg/kg every 6 hours	Intramuscular/ intravenous	At least 7 days	Consider further oral treatment
Pneumonia in HIV infected or exposed children	Use regimen for severe or pneumonia			At least 10 days	Ceftriaxone as second-line treatment

1.4 RATIONALE FOR DESIGN OF THE PEDICAP TRIAL

Currently there are no robust trial data to:

1. Support the selection of antibiotics for, or demonstrate potential benefits from, rapid step-down to oral antibiotics after initial treatment of severe pneumonia with intravenous antibiotics.
2. Define the optimal overall duration of antibiotic treatment for children with severe pneumonia initially requiring hospitalisation.
3. Confirm that currently recommended doses for amoxicillin, the most common oral antibiotic used to treat childhood pneumonia, are adequate when used in this indication in a twice daily regimen in populations with a high prevalence of comorbidities, including malnutrition.

The PediCAP trial has been designed specifically to address each of these three areas within one overarching study, increasing efficiency.

1.4.1 Rationale for Design of Oral-step Down Comparisons

First, rapid step-down to oral antibiotics would enable earlier discharge from hospital and reduce risks of nosocomial infections/acquisition of resistant bacteria. While step-down treatment with **oral amoxicillin** may be effective, **oral co-amoxiclav**, a combination of amoxicillin and the beta-lactamase inhibitor clavulanate, is an alternative that will also treat MSSA and respiratory Gram-negative bacteria, maintaining the advantage of the broader spectrum offered by the intravenous regimens. This is particularly pertinent considering the current global and African context of increasing antimicrobial resistance. An advantage of using co-amoxiclav is that dosing regimens can closely follow those of amoxicillin, while a disadvantage could be a higher rate of antibiotic-associated diarrhoea [31]. Within the main trial (PediCAP-A), this question regarding relative benefits and risks of step-down with oral amoxicillin vs co-amoxiclav will be made by using a standard 1:1 randomisation, and comparison with the hypothesis that oral co-amoxiclav will be superior to oral amoxicillin.

However, different ratios of the two component drugs in co-amoxiclav are used worldwide and there are no data to support which might be optimal. For the main comparison above, we will use the 7:1 amoxicillin:clavulanate ratio which is the European Medicines Agency (EMA) approved ratio for twice daily dosing of co-amoxiclav in children, and is most widely used worldwide. However, the 14:1 ratio might achieve broadly similar clavulanate levels with fewer side-effects whereas the 4:1 ratio formulation might achieve greater clavulanate levels and potentially greater efficacy. In a parallel Phase II pharmacokinetic trial (PediCAP-B), we will therefore evaluate the drug concentrations of amoxicillin and clavulanate achieved when 4:1, 7:1, and 14:1 ratios of co-amoxiclav are used twice-daily in children with severe pneumonia. Rates of antibiotic-associated adverse events will also be compared between these groups.

1.4.2 Rationale for Design of Antibiotic Duration Comparisons

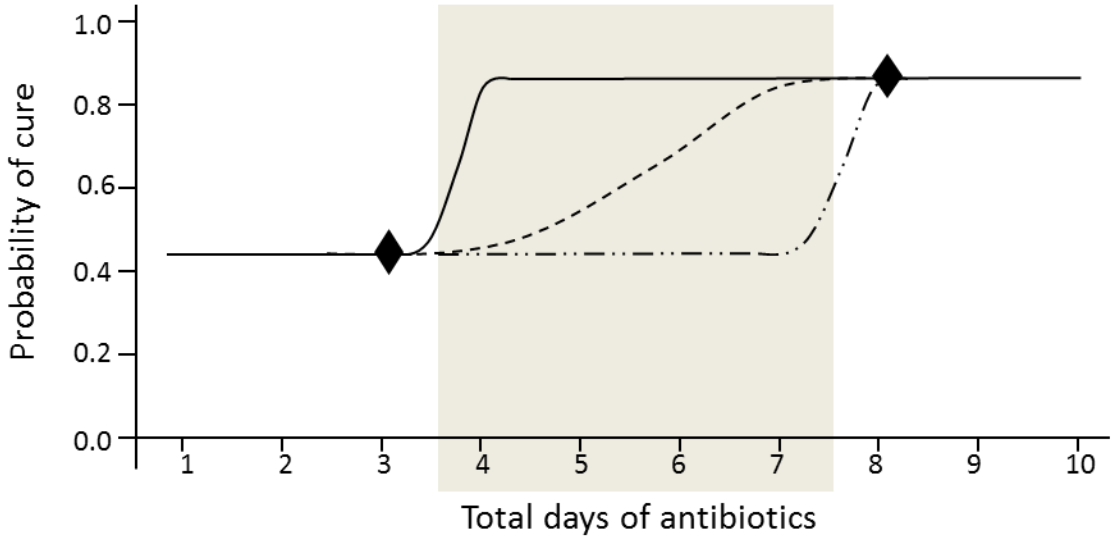
A shorter duration of total antibiotic exposure could reduce unwanted side effects and would be highly desirable if cure rates were similar. Further, duration of exposure is almost certainly an important influence on the microbiome as longer treatment courses represent greater selection pressure on commensal flora. In addition to higher rates of antibiotic-associated diarrhoea, co-amoxiclav may also be associated with higher impact on the microflora than amoxicillin, including greater selection of resistant colonizing bacteria. For any child, antibiotic therapy presents a trade-off: treating the current infection increases the risk of infections in the subsequent months being caused by antibiotic resistant bacteria [32]. Especially when considering broader-spectrum antibiotics for common severe childhood infections, such as severe pneumonia, it is therefore essential that the optimal duration of treatment that delivers effective cure rates, while reducing toxicity and the selection of resistant colonising bacteria is identified.

There is no oral step down recommendation in the current WHO guidance for treatment for severe pneumonia, but total treatment durations for intravenous antibiotics of between 5-7 days are generally recommended internationally, and 4-5 days is the modal duration of intravenous antibiotics in several of the planned trial sites (see **Section 1.4.4**). Within PediCAP, we will identify the optimal total duration of antibiotic therapy using a multi-arm randomised design. The reason for randomising to total duration of therapy (accepting that IV duration is likely to vary between 1-3 days) is because this is what would be recommended in any future amendment to WHO community-acquired pneumonia guidelines and is most generalisable outside the trial.

The standard method of comparing different durations of therapy is to compare two arbitrary durations using a non-inferiority design. The major challenge with this approach is that there is no guarantee that either of these two durations are optimal – in particular, if the shorter duration is inferior to the longer duration, such a trial provides no information about durations between the two chosen for comparison. For example, in **Figure 3**, a hypothetical trial comparing 3 days versus 8 days of total antibiotic duration (black diamonds only) cannot provide any information on rates of outcomes with 4-7 days of antibiotic therapy.

In reality, associations between duration of total antibiotic treatment and outcomes follow a "duration-response" curve: that is, each additional day of antibiotic treatment will increase the probability of an individual child experiencing a good (e.g. cure) or bad (e.g. toxicity, development of resistance) outcome by some amount. This is illustrated by the lines that join the two cure rates observed in a hypothetical trial comparing 3 vs 8 days total duration of antibiotics in **Figure 3**. At some point in the "duration-response" curve, each additional day will have at most a very small effect on the outcome, and the "duration-response" curve will reach an asymptote, the highest possible rate of the outcome in the population. Given the inherent trade-offs between the risks and benefits of antibiotics, the optimal duration of antibiotics may be considered the smallest duration such that efficacy is very close to this maximum, whereas toxicity and resistance development are far from their maximum. However, as above, any two cure rates observed by comparing only two durations of therapy (3 vs 8 days in **Figure 3**) are compatible with many different "duration-response" curves. In practice, if the true "duration-response" curve is reflected by the solid black line, we would likely recommend 4 days of treatment, whereas for the short-dashed line we might recommend 7 days and for the long-dashed line 8 days.

Figure 3: Example of cure rates with different durations of antibiotic therapy



Note: diamonds illustrate the results that might be obtained from a hypothetical two-group trial randomising children to 3 vs 8 days, whereas no information about cure rates in the gray box can be obtained from such a

trial. Lines indicate different relationships between duration of antibiotic treatment and response that are all compatible with the same observed cure rates with 3 and 8 days of treatment, that would lead to different recommendations regarding "optimal" durations of treatment.

Rather than picking two arbitrary durations, in PediCAP we will therefore randomise children to multiple different durations in order to estimate the actual "duration-response" curve for primary and secondary outcomes [33] (**Figure 3**). Doing this means we can estimate this curve overall and according to specific characteristics, such as age, clinical severity and underlying disease (e.g. HIV-infected/exposed, malnutrition). This will enable us to estimate precisely durations at which specific rates of clinical cure are achieved, and where the "duration-response" curve "flattens off", meaning that additional antibiotic exposure is no longer adding relevant clinical benefit. As above, this approach is much more efficient than arbitrarily choosing two durations and comparing them in a standard superiority or non-inferiority trial [33].

In terms of choice of the minimum and maximum total durations which will be included in the randomisation, seven to eight days are the currently recommended maximum duration of treatment with intravenous antibiotics for suspected staphylococcal pneumonia, with three days considered the minimum treatment duration for non-severe pneumonia in areas with low HIV prevalence. There is interest in, and some adult data supporting, effectiveness of shorter antibiotic durations [34, 35], hence the lowest total duration considered will be **4 days**. As there is the theoretical possibility that children may do less well on oral antibiotics, the maximum considered treatment duration will be **8 days**. Thus, in PediCAP children who step down to oral antibiotics will be randomised 1:1:1:1:1 to 4 vs 5 vs 6 vs 7 vs 8 days total duration of antibiotics using a factorial design.

1.4.3 Rationale for Inclusion of "Benchmarking" Continuous Intravenous Group

The challenge with antibiotic trials is identifying an appropriate "standard of care", since current practice is often very variable in terms of both drug and duration, reflecting local opinion as well as local resistance patterns. However, were the trial to only include the durations above, even if we estimate the "duration-response" curve for each of amoxicillin and co-amoxiclav oral step-down, it would be reasonable to ask how these curves related to continuing on intravenous antibiotics for the whole duration of treatment, particularly since WHO guidance currently has variable recommendations for the duration of injectable antibiotics for severe pneumonia ranging from at least 5 to at least 10 days.

We will therefore add an 11th randomised group which will receive **5-day intravenous antibiotics with no oral step-down**. Hospitals participating in PediCAP who undertook a short epidemiological survey identified that more than 50% of children started on intravenous antibiotics for CAP stayed in hospital for at least 4 days or longer (see **Section 1.4.4**). The choice of five days is also in accordance with the minimal WHO recommendation, although clinical practice varies. As standard-of-care is variable, this is not a formal control group, but will enable the trial to "benchmark" the duration-response curve for each oral step-down option.

1.4.4 Service Evaluation in Recruiting Sites

To inform protocol development, a short service evaluation was conducted in four of the five trial sites (South Africa, Uganda, Zambia and Zimbabwe) in February 2018. Brief details of consecutive children aged 2 months to 10 years admitted for antibiotic treatment of pneumonia were recorded for 2 weeks or 30 children, whichever was achieved first. In total, 93 children were recorded across the sites (12-32 children/site). Of these, 79 (85%, 40/79 males) children were commenced on intravenous antibiotics at admission to hospital. The commonest intravenous regimens were those recommended by the WHO and included in the eligibility criteria below (56/79 – 71% -

benzylpenicillin or ampicillin plus aminoglycoside; 12/79 – 15% - ceftriaxone or equivalent third generation cephalosporin). The modal duration of hospitalisation was 4 days, and 47/79 (59%) children were hospitalised for 4 days or longer. Only 6/79 (8%) children were discharged from hospital without further oral antibiotic treatment, and half of these had been treated in hospital for 7 days or longer already. Further relevant results for the 79 children treated with intravenous antibiotics are summarised in **Table 3** below.

Table 3: Additional details of 79 children treated with intravenous antibiotics in trial sites

VARIABLE	SUMMARY			
Age (in months)	Median	IQR	Min	Max
	12	6-18	3	98
Weight (in kg)	Median	IQR	Min	Max
	7.8	6.6-9.3	2.9	22.2
	Children weighing <4kg n=3			
Underlying disease/risk factor	Malnutrition	HIV exposure	Chronic neurological disease	HIV infection
	13/79 (16%)	7/79 (9%)	6/79 (8%)	3/79 (4%)
Investigations	Chest X-ray obtained		Inflammatory marker measured	
	31/79 (39%)		63/79 (81%)	
Supportive therapies during stay	Supplemental Oxygen	IV fluids	Nasogastric feeds/fluids	
	51/79 (65%)	14/79 (18%)	5/79 (6%)	

Note: IQR=interquartile range.

1.4.5 DOSING FOR PEDICAP

National and international amoxicillin dosing guidelines vary considerably (**Table 4**) and often target a constant mg/kg/day range, which does not account for clearance rates differing by both weight (allometry) and age (maturity).

Table 4: International guidelines for oral amoxicillin and co-amoxiclav dosing for CAP in children from 2 months to 12 years

DRUG	GUIDELINES	DAILY DOSE	Hours between doses
Amoxicillin	Blue Book [36]	45-90 mg/kg/day	8
Amoxicillin	BNFC [37]	375-1500 mg/day	8
Amoxicillin	NCDC [38]	20-50 mg/kg/day	6-8
Amoxicillin	Red Book [39]	80-100 mg/kg/day	8
Amoxicillin	RSA EML [40]	90 mg/kg/day	8
Amoxicillin	WHO Pocket Book [27]	80 mg/kg/day	12
Amoxicillin	WHO 2014 guidelines [30]	2-6 dispersible tablets (250mg) /day	12
Co-amoxiclav 4:1	Blue Book [36]	0.45-1.5 ml/kg/day	8
Co-amoxiclav 7:1	Blue Book [36]	0.3-0.4 ml/kg/day	12
Co-amoxiclav	BNFC [37]	0.75-0.45 ml/kg/day	8
Co-amoxiclav	NCDC [38]	40 mg/kg/day	12
Co-amoxiclav 4:1	Red Book [39]	20-40 mg/kg/day	8
Co-amoxiclav 7:1	Red Book [39]	25-45 mg/kg/day	12
Co-amoxiclav 14:1	Red Book [39]	90 mg/kg/day	12
Co-amoxiclav	WHO Pocket Book [27]	No information	

Note: *The Manual of Childhood Infections: The Blue Book (4th Edition)* is endorsed by the Royal College of Paediatrics and Child Health and European Society of Paediatric Infectious Diseases and is a leading handbook used in Europe [36]. The *British National Formulary for Children (BNFC),* last published in 2017, is a commonly used paediatric reference for prescribing in the United Kingdom [37]. *Red Book (2018): Report of the Committee on Infectious Diseases (31st Edition)* is endorsed by the American Academy of Pediatrics Committee on Infectious Disease [39]. The WHO Pocket book of hospital care for children (2013) is part of a series of documents and tools that support the Integrated Management of Childhood Illness (IMCI) [27]. The Republic of South Africa's *Paediatric Hospital Level Standard Treatment Guidelines and Essential Medicines List (EML)* (2013) were developed by an Expert Review Committee, National Essential Medicine List Committee and external stakeholders involved in paediatric care [40]. The Indian *National Treatment Guidelines for Antimicrobial Use in Infectious Diseases* were developed by the National Centre for Disease Control (NCDC) and were published in 2016 [38].

Dosing choice should aim to maximise coverage of all potential causative bacteria, including penicillin-resistant pneumococci and *Staphylococcus aureus*. However, dosing is constrained by the strengths of the currently available formulations. Oral solutions can be dispensed to target a specific mg/kg, but can be complex for caregivers to administer outside of hospital and often require refrigeration (e.g. oral co-amoxiclav solution). Without refrigeration, there is significant degradation of clavulanate in settings of higher ambient temperatures, leading to markedly reduced levels in the dispensed syrup form after approximately 5 days [15]. Dispersible tablets are a more practical formulation, being less bulky to transport and store, easy to administer in weight-band based doses and not requiring a cold-chain. Experience with providing dispersible antiretroviral tablets to even young HIV-infected children demonstrates high acceptability [41], and dispersible amoxicillin is already recommended by WHO for non-severe CAP (i.e. fast breathing or fast breathing and chest indrawing without danger signs [30]) in children from 4–19kg (

Table 5). For the comparisons in the main trial (PediCAP-A), the Marketing Authorisation holder for paediatric oral suspension twice daily 7:1 co-amoxiclav formulation (Sandoz) has agreed to provide dispersible tablets of amoxicillin (250 mg) and co-amoxiclav (7:1 ratio amoxicillin:clavulanate; 200/28.5 mg).

Figure 4: Degradation over time of amoxicillin and clavulanate in oral solution under different in-house storage conditions (ambient temperatures)

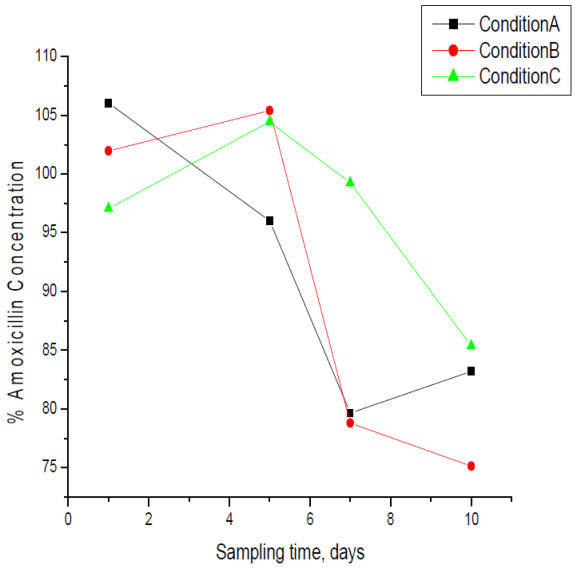


Fig.1: Degradation of amoxicillin versus time period under different in –home storage conditions.

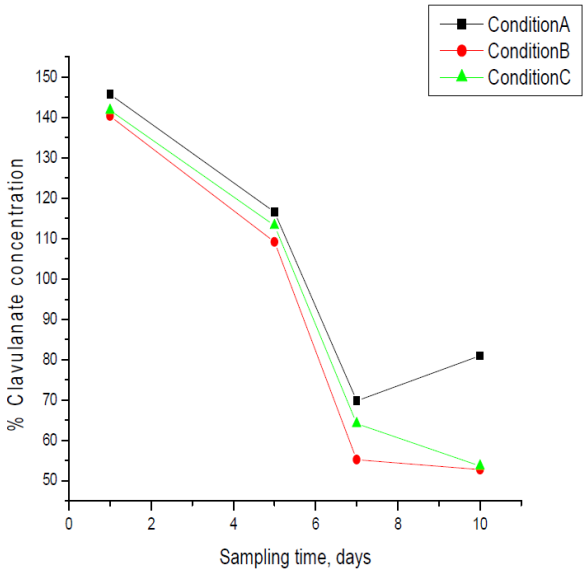


Fig. 2: Degradation of clavulanate versus time period under different in –home storage conditions.

Note: reproduced from [15].

Table 5: WHO 2014 guidelines for oral amoxicillin treatment of non-severe pneumonia [30]

Weight band (kg)		Number of 250mg oral amoxicillin tablets/day	
Lower	Upper	Fast breathing pneumonia	Fast breathing & chest indrawing pneumonia
4	<10	2	2
10	<14	4	4
14	19	4	6

Unbiased treatment comparison in the trial requires as similar amoxicillin doses in each group as possible, and a simple dosing strategy requires twice-daily dosing by weight-bands. We elected to enable more dosing options by allowing uneven numbers of tablets (3, 5, etc.) to be given daily, with the highest dose being given in the morning.

For PediCAP we therefore calculated target amoxicillin daily dose for each weight using a dosing calculator by Denti et al. [42] incorporating allometry and maturity (maturation parameters estimated by Barker et al. [43]) targeting expected exposure in a 40-kg adult receiving 3000 mg daily (75 mg/kg/day). We used the widely used paediatric HIV weight banding to include children from 3-35kg and for simplicity for physicians. Actual daily dose was chosen to be as close to the target as possible, aligning with WHO 2014 pneumonia guidelines [30] where possible. Co-amoxiclav 7:1 dosing was matched to amoxicillin doses as closely as possible.

From these calculations, incorporating allometry and maturity, the maximum target daily dose in mg/kg was 99 mg/kg in children weighing 12kg (**Figure 5A**). The lowest target daily dose in children above 12kg was 78 mg/kg whereas in children less than 12kg the lowest target daily dose was 43 mg/kg (**Figure 5A**). Consequently, within each weight band, the largest differences in target dose were seen in the lightest children.

Dosing choices were most constrained in the lighter weight-bands, as one-tablet dose changes have large effects in mg/kg. We chose to increase the number of tablets given to the lightest children above that computed by the dose tool to enable twice-daily dosing (**Figure 5A**), and to match with WHO 2014 for children weighing 4-<6kg. Children weighing 3-<4kg are not included in WHO 2014 recommendations and will receive between 128 and 167mg/kg/day amoxicillin in PediCAP, compared to the 125mg/kg/day recommended by WHO 2014 for 4kg children. Although renal injury has been described in children after accidental amoxicillin overdose, this is rare even in single doses above 250mg/kg [44], which is much higher than the highest daily dose in PediCAP.

The biggest differences in dose between amoxicillin and co-amoxiclav was also seen in the lightest children (**Figure 5B**), where co-amoxiclav dose was 20% lower than amoxicillin, again due to constraints required by having integer numbers of tablets in each dose. Dosing in other weight bands differed by a maximum of 7%.

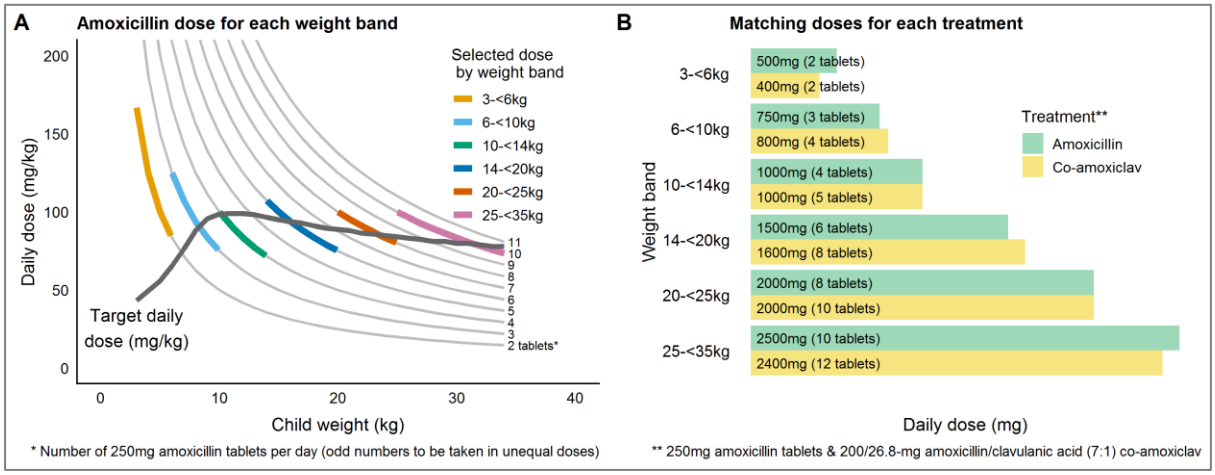
PediCAP oral amoxicillin 250mg dosing differs from WHO 2014 in three ways:

1. The smallest child is 3kg rather than the 4kg in WHO 2014. Dosing for the 3kg children is PediCAP is the same as 4kg children in WHO 2014. In practice, the number of 3-4kg children aged 2 months or older is anticipated to be small (eg **Table 3**), but PediCAP uses a 3kg lower weight band to align with the HIV weight bands.
2. The largest child is 35kg rather than 19kg in WHO 2014. These heavier children will receive higher absolute doses but the pattern of increasing by two tablets per day in each weight band remains. Inclusion criteria for PediCAP require children to weigh <=30kg at randomisation, but theoretically they could increase weight by the time they switch to oral

treatment (e.g. due to correction of dehydration). In practice the number of children aged 6 years or younger weighing 30kg is likely to be very small.

3. Dosing for children 6-<10kg is 3 tablets per day in PediCAP rather than 2 tablets per day in WHO 2014. This is because the risk of under dosing children in this weight-band judged too great when balanced against the benefit of aligned dosing.

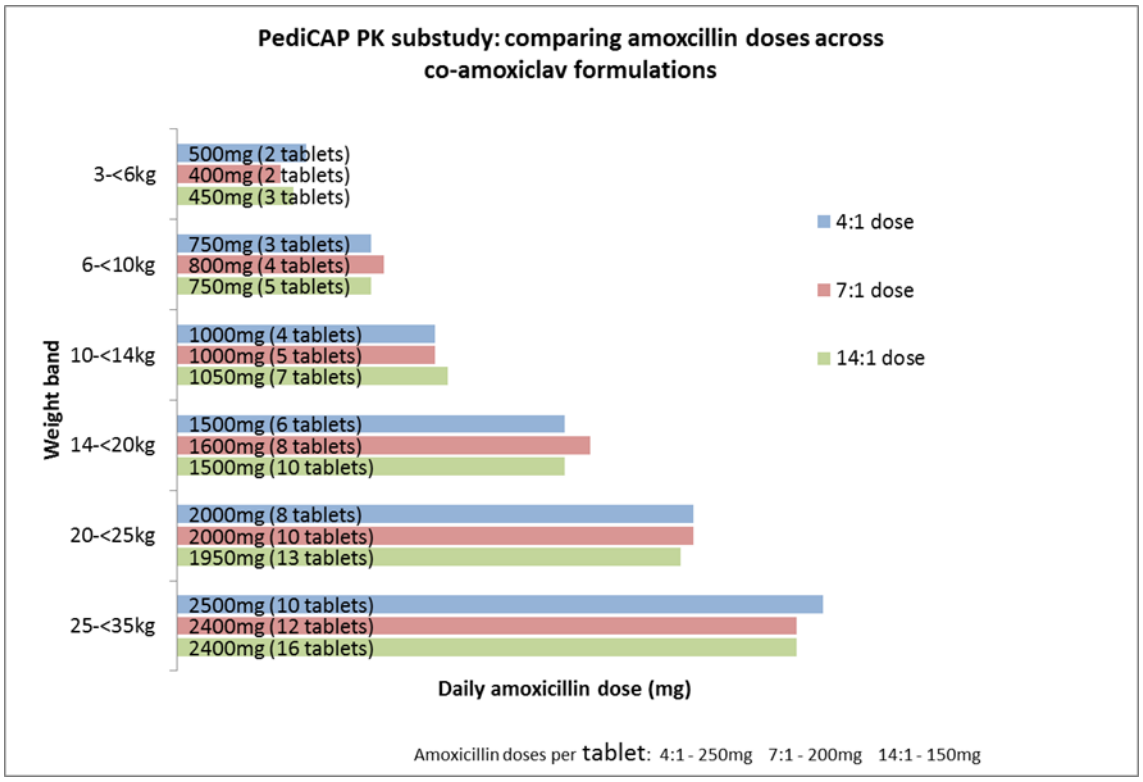
Figure 5: Dosing options



See **Section 5.3.1** for final dosing table for amoxicillin and co-amoxiclav 7:1.

The formulations of the 4:1 and 14:1 tablets are 250/62.5 mg and 150/10.725 mg of amoxicillin/clavulanate, respectively. The dosing scheme for the 4:1 formulation was the same as amoxicillin alone (as both contain 250mg amoxicillin). For 14:1 co-amoxiclav, the dosing scheme was chosen to be as close as possible to the 4:1 dosing (**Figure 6**). See **Section 5.3.1** for final dosing table for co-amoxiclav 4:1 and 14:1.

Figure 6: Co-amoxiclav dosing choices: comparing amoxicillin doses across co-amoxiclav formulations



1.5 OBJECTIVES OF PEDICAP

The overarching goal is to optimise the treatment of CAP in children in sub-Saharan Africa.

Recognising the cost of conducting large trials, and the limited number that will ever be performed in children compared to adults, the trial design will maximise the value that can be gained – firstly, by including two factorial randomisations within the clinical trial to address questions about both specific drug for oral step-down antibiotics and the total duration of antibiotic therapy; secondly, by including multiple parallel substudies nested within the trial.

For children aged 2 months to 6 years inclusive weighing 3-30kg hospitalised with severe CAP treated as inpatients in South Africa, Uganda, Zambia and Zimbabwe, the specific objectives of the PediCAP trial are therefore to answer the following specific questions:

1. Is the rate of clinical cure superior with co-amoxiclav 7:1 versus amoxicillin oral step-down therapy? (co-primary objective)
2. What is the optimal antibiotic treatment duration that achieves good rates of clinical cure whilst minimising length of hospital stay, toxicity and acquisition of multidrug antimicrobial resistance? (co-primary objective)
3. Does this optimal duration vary by key characteristics, such as age, underlying conditions or risk factors such as HIV exposure, malnutrition or severity, suggesting that antibiotic selection or duration should be personalised to specific subgroups? (secondary objective)
4. What plasma exposures of amoxicillin and clavulanate are achieved with standardised allometric-based dosing of co-amoxiclav in 4:1, 7:1 and 14:1 dispersible tablets, and do any have significant advantages in terms of PK or toxicity? (secondary objective)

PediCAP will therefore develop an evidence-base for recommending oral step-down antibiotic treatment and future choice of drug, dose, duration and delivery formulation that achieves resolution of symptoms of severe CAP while minimising the acquisition of resistant bacteria.

2 SELECTION OF SITES/CLINICIANS

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

PediCAP will be conducted at 5 sites and their satellite hospitals:

- University of Witwatersrand, Johannesburg, South Africa
- Africa Health Research Institute and University of Kwa-Zulu-Natal, South Africa
- Mulago National Referral Hospital and Makerere University College of Health Sciences, Kampala, Uganda
- University Teaching Hospital, Lusaka, Zambia
- Parirenyatwa and Harare Central Hospitals and the University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe

No additional sites will be selected. The recruitment target is 220 children at each site. However, the goal of the trial is to recruit overall, and individual site targets may be modified as needed to achieve this.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

Once a site has been identified as being compliant with the inclusion criteria (and not excluded), the trial team will provide the site with a copy of this protocol, a trial summary and the Summary of Product Characteristics (SPC) or Investigator Brochure (IB; if applicable).

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

Sites where a previous serious protocol breach has occurred will be visited and thoroughly reviewed before allowing children to enter the trial.

Those sites that meet the criteria will be issued with the PediCAP master file documentation for their Site-specific Approval (SSA) and CTU accreditation documents.

2.1.1 PI's Qualifications & Agreements

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the Research Ethics Committee (REC) or Institutional Review Board (IRB), and/or the regulatory authority(ies).

2. The investigator should be thoroughly familiar with the appropriate use of the investigational products, as described in this protocol, in the current IB, in the product information and in other information sources provided by the Sponsor.

3. The investigator should be aware of, and should comply with, the principles of Good Clinical Practice (GCP) and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.

4. The investigator/site should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority(ies).

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

6. 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 children within the agreed recruitment period (that is, the investigator regularly treats the target population).

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

3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4. 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.

5. The site should have sufficient data management resources to allow prompt data return to the CTU (refer to the Data Management Plan for timelines). Sites that have previously participated in CTU-coordinated trials should have a proven track record of good data return.

2.1.3 Site Assessment

Each selected clinical trial site must complete an Investigator Statement, Signature and Delegation of Responsibilities Log, and provide staff contact details.

The Investigator Statement verifies that the site is willing and able to comply with the requirements of the trial. In PediCAP the Investigator Statement is within the Clinical Trial Agreement. This 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 CTU. The CTU 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 Trial Master File (TMF) at the site and also at the CTU.

2.1.4 Source Data

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's study subjects. Source data are contained in source documents and are defined by EU guidelines as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data is recorded. Source documents can include hospital records, clinical and office charts, laboratory notes, x-rays, and pharmacy dispensing records. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data

should be traceable, should not obscure the original entry, and should be explained if necessary (ie. via an audit trail). Each data element should only have one source.

In PediCAP, the CRF will be the source document for all data elements on the following CRFs:

- CRF07 Antibiotic Acceptability
- CRF15 Household Socioeconomic
- CRF16 Cost to Families for Care and Treatment.

These CRFs document questions that should be asked to the parents/carers in an interview and therefore answers can be recorded directly on to the CRF.

All data recorded on all other PediCAP CRFs should be verifiable in the source documents.

2.2 APPROVAL AND ACTIVATION

On receipt of the above documents at the CTU, written confirmation will be sent to the PI.

1. The site should conduct the trial in compliance with the protocol as agreed by the Sponsor and, if required, by the regulatory authority(ies), and which was given favourable opinion by the REC and/or IRB.
2. The PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the CTU.

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

3 SELECTION OF CHILDREN

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the child.

The eligibility criteria are the standards used to ensure that only medically appropriate children are considered for this study. Children not meeting the criteria should not join the study. For the safety of the children, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other children with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

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.

3.1 CHILD INCLUSION CRITERIA

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

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

For children enrolled in PK (**Section 10.1**) or microbiology (**Section 10.2**) substudies, additional inclusion criteria are:

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

10. If undergoing additional microbiological sampling: willing to provide samples at enrolment, discharge and week 4 (separate consent will be obtained for microbiological sampling which may be refused and the child still join the main trial (PediCAP-A))

The inclusion criteria are broad, being deliberately designed to identify the population to whom results would be generalised (children with severe CAP). Severity is pragmatically defined by the physician judging that the child needs intravenous antibiotics – since this involves risks from intravenous access and prolongs hospital stay, this is not undertaken lightly – together with WHO 2014 criteria for severe pneumonia [28] supplemented by an additional recommended danger sign from a consensus committee (moderate/severe malnutrition)[45], with signs of pneumonia defined following the 2013 WHO Pocketbook of hospital care for children [27]. Chest X-ray is not required for inclusion, but results will be collected where available.

11. Whilst many previous studies have excluded over-five year-olds, this – and any other age threshold – is arbitrary; pneumonia management and response in 4-, 5- and 6-year olds would not be expected to differ clinically. Data show that 3/79 (4%) included children treated initially with intravenous antibiotics in PediCAP sites were older than 5 years (**Section 1.4.4**). It is likely that in the absence of additional guidance, many centres in LMICs use the same regimens for over-fives as they do for under-fives. Furthermore, based on our experience with a UK-based trial (ISRCTN76888927), combined age and weight-based inclusion and exclusion criteria are more appropriate, in particular when weight-banded dosing will be used. In this UK trial, roughly 10% of the first 230 recruited children were older than 5 years of age, but were nonetheless eligible on the basis of weight criteria and planned antibiotic management after discharge home. We therefore plan to use predominantly weight-based exclusion criteria (based on the dosing weight-bands in **Body weight** should be obtained by ward nurses, using standard methods (as to determine the doses of intravenous antibiotics). Body weight reported by parents is not acceptable. Additionally, body weight should be measured on the day of switch to oral antibiotic to assign the child to the correct weight-band dosing schedule, as weight may change considerably since admission (e.g. if the child was dehydrated at the time of enrolment into the study).

3.1.1.A Criteria for Moving from Intravenous to Oral Antibiotics

The main criteria for moving from intravenous to oral antibiotics is that the child should have improved clinically, be currently clinically stable or continuing to improve, and be well enough to take medication by mouth, i.e. can ingest and keep down the dispersible tablets when made up in a small amount of liquid, and hence oral absorption of the antibiotic is likely to be good. Children may move to oral medication whilst inpatients (e.g. if they are still receiving supplemental oxygen). See MOP for further details.

Children should be discharged on oral medication as soon as they are clinically stable and have received and retained at least one dose of oral antibiotics. See MOP for further details.

Table 7 below) rather than restricting to under 5 year olds, since in practice this will be how results from the trial will be applied, increasing its generalisability.

3.2 CHILD EXCLUSION CRITERIA

1. Point-of-care semi-quantitative C-reactive protein (CRP) test < 10mg/l at screening (very unlikely to represent severe pneumonia requiring antibiotics)
2. Likely nosocomial pneumonia (onset >48h post-admission)
3. Admitted to hospital overnight in the last 28 days (possibility of nosocomially-acquired pneumonia)
4. Known or anticipated need for invasive ventilation or admission to intensive care
5. Clinician considers this episode to be predominantly due to reactive airways disease (e.g. asthma) (wheeze responsive to bronchodilators, see Manual of Operations (MOP) for more details)
6. Clinician considers this episode to be due to viral bronchiolitis alone in a child under 1 year
7. Documented allergy to any drug from the penicillin class or contra-indications to penicillin/amoxicillin/co-amoxiclav
8. Anticipated need for systemic treatment with an antibiotic other than trial regimens during hospital admission or in the following 28 days (e.g. for *Pneumocystis jiroveci*)
9. On long-term antibiotics for prophylaxis or treatment (e.g. for tuberculosis treatment or cotrimoxazole prophylaxis for HIV infection)
10. Previously enrolled in PediCAP

A semi-quantitative point-of-care CRP test will be used to exclude children with very low CRP who are extremely unlikely to have a bacterial infection requiring antibiotics. This is to avoid including a large number of children in the trial without bacterial infections (who therefore do not need antibiotics) and hence potentially miss important effects in children with bacterial infections. CRP testing will be standardised using a point-of-care device which can be done using a finger or heel prick rather than requiring an additional venous blood draw. Its lowest category is <10mg/l and only children in this category will be excluded. If children also have CRP measured in the laboratory, the value from the semi-quantitative test will be used to determine eligibility, since this should be done for all children in the trial. If, for any reason, the semi-quantitative test cannot be used (i.e. is missing), then a laboratory CRP value may be used instead to determine eligibility.

HIV-exposed but uninfected children and those with malnutrition may be included in the trial, as may HIV-infected children provided they are not on long-term cotrimoxazole (exclusion criterion 9). HIV testing will follow standard practice at each site. Other exclusion criteria reflect children without CAP, or in whom the step-down options based on amoxicillin would be contra-indicated, or in whom other oral antibiotics are needed (which could dilute any differences between children randomised to oral amoxicillin vs co-amoxiclav step-down).

It is anticipated that a substantial proportion (~50%) of children will have received a small number of doses of oral/intramuscular antibiotics in the community for this illness. Reflecting what would be recommended in national and international guidance after the trial, these children will be eligible, and the treatment durations compared will be from the start of intravenous antibiotics. Prior oral/intramuscular antibiotics for this illness before hospitalisation will be considered in subgroup analyses.

3.3 NUMBER OF CHILDREN

The total number of children recruited in the main trial (PediCAP-A) and the Phase II PK trial (PediCAP-B) will be 1,220. Each child will be approached for recruitment into either PediCAP-A or PediCAP-B.

3.3.1 MAIN TRIAL (PEDICAP-A)

A total of 1,100 children meeting eligibility criteria above will be recruited into the main trial (PediCAP-A). Randomisation will be stratified by site (5 sites each recruiting 220 children).

3.3.2 PK SAMPLING

A total of 180 children will undergo intensive PK sampling. Of these 180, 60 will be main trial children (in PediCAP-A) who were randomised to oral co-amoxiclav 7:1 step-down (see **Section 10.1.1**). These should be children randomised to co-amoxiclav in the main trial; however, additional consent will be sought for this, which may be refused and children still join the main trial. In total 60 of the 500 children randomised to co-amoxiclav 7:1 in PediCAP-A will undergo PK sampling.

An additional, but separate, 120 children meeting the same eligibility criteria above will undergo randomisation to two different co-amoxiclav formulation strengths, 4:1 vs 14:1, and undergo intensive PK sampling in a parallel Phase II PK trial (PediCAP-B) (see **Section 10.1.2**). These children will receive 6 days total antibiotics (the median in the main trial). This randomisation will not be stratified by site, but will be stratified by weight-band. All other investigations and follow-up will be identical.

3.3.3 MICROBIOLOGICAL SAMPLING

A total of 330 children from the main trial (PediCAP-A) (66 per site) will undergo microbiological sampling; additional consent will be sought for this, which may be refused and children still join the main trial. These children will be asked to provide additional samples at baseline, discharge and week 4 follow-up. Children will be randomised as part of the main trial (PediCAP-A).

3.4 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.3**.

3.5 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

Potentially eligible children for PediCAP-A and PediCAP-B will be identified prior to completing 24h of intravenous antibiotics, ideally at the time intravenous antibiotics are initiated. Parents/carers of potentially eligible children based on clinical inclusion and exclusion criteria will be given a short information leaflet on the trial. If interested, they will then be given a concise information sheet relating to screening for the PediCAP trial and will be asked to give written consent before trial-specific point-of-care CRP testing (using an additional finger or heel prick or as part of a routine care blood draw). Parents/carers of eligible children (requiring CRP >10mg/l) will then be given an information sheet about the full PediCAP trial and asked to give written consent before any further trial-specific procedures, including randomisation, are performed or any further samples are taken for the trial. Separate information sheets will be used for PediCAP-A and PediCAP-B because PediCAP-B does not include a randomisation to total duration of antibiotic therapy and because all children in PediCAP-B undergo PK sampling and consent must be provided for this. Each child will be

approached for recruitment into either PediCAP-A or PediCAP-B (not both and not sequentially). Signed consent forms (screening and trial entry) must be kept by the investigator and documented in the case record form (CRF)\worksheet and a copy given to the child or family.

It will be made completely and unambiguously clear that the child and/or parent/carer of the 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 child's treatment. See **Section 0** for more details on procedures around child withdrawal from the trial.

Eligible children should be randomised as soon as possible and prior to completing 24 hours of intravenous antibiotics (that is, the first dose of any intravenous antibiotics must have been administered no more than 24h previously at the point of randomisation). Confirmation of eligibility criteria and written informed consent must be obtained before randomisation.

Children in the microbiological substudy should have nasopharyngeal and peri-rectal swabs taken as soon as possible after consent for the full trial. This is in order to assay baseline commensal flora, including presence of any resistance genes, as early as possible in the antibiotic treatment course. If a child is wearing a nappy, or passes a stool, a sample of faecal material may be taken instead of a peri-rectal swab.

4 REGISTRATION & RANDOMISATION

Randomisation for the main trial (PediCAP-A) will be stratified by site (5 sites, each recruiting 220 children). Randomisation into the Phase II PK trial (PediCAP-B) will be stratified by weight-band only (120 children – 60 per co-amoxiclav ratio across the six weight-bands). Children will be recruited to either the main trial (PediCAP-A) or the Phase II parallel PK trial (PediCAP-B). See the MOP for more details of registration procedures.

Children will be recruited from the paediatric emergency departments and wards of the site hospitals, and will be randomised before they have received any more than 24h of intravenous antibiotics, as described above.

Before randomisation, the participant's eligibility for enrolment will be confirmed (**see Section 3**). Parents/carers must confirm that they have read the relevant patient information sheet and have provided written informed consent to enter into the trial.

Baseline assessments will be performed as summarised in the Trial Assessment Schedule, **Table 1**, including recording of vital signs and clinical characteristics relevant to this episode from the medical notes. Results of any blood tests (haematology, biochemistry), microbiology and chest X-rays done as part of standard clinical care will also be recorded, but are not required for trial enrolment. Where possible, and wherever these are available for standardised assessment, digital versions of chest X-rays will be collected for the trial.

Children enrolled in the microbiology substudy should have a nasopharyngeal specimen and peri-rectal swabs taken for analysis of commensal flora as soon as possible after trial consent (i.e. as close to initiation of intravenous antibiotics as possible). If a child is wearing a nappy, or passes a stool, a sample of faecal material may be taken instead of a peri-rectal swab.

The clinician should complete the Baseline Form and send for data entry directly onto the secure web-based trial database.

Clinical assessment should be scheduled by telephone for one, two, and three weeks post randomisation and face-to-face for four weeks post randomisation. Assessment in any week can be face to face if this is standard practice.

A trial register will be kept at the clinical site and will record all children who are eligible and invited to join the trial. Those accepting will have initials, date of birth, randomisation date and Study ID recorded. Those who refuse will have initials, date of admission, age (months or years), and reason for refusal recorded. The register will be kept in a secure place in each clinical site; must be available for monitoring, audit and inspection; and will be the responsibility of the Principal Investigator at that site.

4.1 RANDOMISATION PRACTICALITIES

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

Randomisation will be performed online. To randomise a child the information contained on a completed randomisation CRF\worksheet will be entered into the online trial database accessible from the local clinical sites that will automatically check for eligibility. Only children with completed

and verified randomisation CRFs\worksheets on the database will be able to be randomised. The computer-generated sequentially numbered randomisation lists will be securely incorporated within this online trial database, and allocation concealed until the point of the next randomisation. Allocation will be made after eligibility has been confirmed by local site staff through the online database. Only the next randomisation will be provided, the remainder of the list will be concealed (ensuring allocation concealment). Delegated member(s) of staff at each site, not directly involved in patient care, will be responsible for carrying out the randomisation process restricted using role-based access. The details of the child's treatment allocation and PediCAP Study ID will be notified to clinical staff, and the Study ID and allocation cross checked between those randomising and those managing the child clinically.

If the site's internet connection is unavailable at the time of randomisation, the child's details can be provided to staff at the CTU by email or phone. At the CTU, staff will verify eligibility and perform the randomisation using the online system. The details of the child's treatment allocation and PediCAP Study ID will be notified to the trial team at the site by email or phone within one hour of the receipt of the randomisation form (during normal working hours).

If the main electronic randomisation system is not working, randomisations will not take place, and this should be recorded as the reason that the child was not randomised.

The child's Study ID and the date of randomisation will be entered into the trial register at the site.

The trial is open-label so there is no need for unblinding.

4.2 CO-ENROLMENT GUIDELINES AND REPORTING

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. within 28 days after randomisation. Participation in observational studies is acceptable in accordance with local guidelines.

5 TREATMENT OF CHILDREN

5.1 INTRODUCTION

All children will initiate treatment with intravenous antibiotics as per the relevant site's standard of care (within the regimens listed in **Section 5.2.1** below) and the eligibility criteria.

In the main trial (PediCAP-A), children will effectively firstly be randomised 5:5:1 to either oral step-down amoxicillin (amoxicillin group); oral step-down co-amoxiclav (co-amoxiclav group); or to remain on intravenous antibiotics (IV group).

Within the amoxicillin and co-amoxiclav groups, children will simultaneously be further randomised 1:1:1:1:1 to receive 4, 5, 6, 7 or 8 days of total antibiotic treatment (from the start of intravenous antibiotic therapy).

Children randomised to the IV group will receive 5 days of treatment with one of the PediCAP standard of care IV antibiotic regimens (see **Section 3.1**). Thus, each child in the main trial will be randomised to one of 11 different groups.

In the Phase II PK trial (PediCAP-B), a separate group of children will be randomised 1:1 to oral step-down with co-amoxiclav 4:1 vs 14:1 (1:1 randomisation ratio) for a total duration of 6 days antibiotics from the start of intravenous antibiotics. Children will be approached for recruitment to either PediCAP-A or PediCAP-B, not both.

Oral treatment will commence when the child is judged well enough to take oral antibiotics, which will be given with food where possible. See **Section** Error! Reference source not found. below for details.

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

- A child randomised to total 8 days antibiotics who is well enough to start taking oral antibiotics after 3 days of intravenous antibiotics will receive 5 days oral antibiotics
- A child who is randomised to total 4 days antibiotics who is well enough to start taking oral antibiotics after 2 days of intravenous antibiotics will receive 2 days oral antibiotics

5.2 INTRAVENOUS ANTIBIOTICS (ALL CHILDREN)

5.2.1 PRODUCTS & TREATMENT SCHEDULE

At the point of randomisation, children should have received no more than 24h of intravenous antibiotics (**Section 3**). However, standard-of-care intravenous treatment should be for at least 24 hours for all children, whether randomised to oral step-down or continuous intravenous antibiotics and regardless of what duration of intravenous antibiotics has been received at the point of randomisation. That is, children randomised to step-down to oral antibiotics should not do so before receiving at least 24h of intravenous antibiotics. Those randomised to intravenous antibiotics will be treated with intravenous antibiotics for 5 days in total (from start of intravenous antibiotics, excluding oral/intramuscular antibiotics received in the community). Parents/carers of children randomised to 5 days' IV will receive travel costs for any additional days their child remains in

hospital solely for the purpose of receiving intravenous antibiotics within the trial, since a few of these children might otherwise be discharged early on oral antibiotics depending on local practice (site-specific).

Dosing should follow the local standards of care (summarised in **Table 6**) which generally follow WHO recommendations where given (**Table 2**). Local standards of care may differ from WHO recommendations due to factors such as local susceptibility patterns, drug availability and institutional prescribing guidelines.

The choice of intravenous antibiotics will be made by the treating physician prior to randomisation. Doses should be given intravenously: if there is a problem with venous access, then isolated post-randomisation doses that should have been given intravenously may be given intramuscularly. Doses will be dispensed from ward stock and prepared and given by the ward nurses. Children will be hospitalised for the entire parenterally administered treatment duration (5 days for those randomised to intravenous antibiotics). After completing their intravenous antibiotics (either after 5 days or after moving to oral-stepdown), children should be discharged as soon as they are clinically stable.

Table 6: Dosing of standard intravenous antibiotics

DRUG	SCHEDULE
Ampicillin	IV/IM: 50 mg/kg every 6 hours
Benzylpenicillin (penicillin G)	IV: 50'000-100'000 U/kg every 6 hours
Cefotaxime	IV: 50 mg/kg every 6 hours or 33.3 mg/kg every 8 hours
Ceftriaxone	IV: 80 mg/kg/d as a single dose once daily OR IV/IM: 50 mg/kg every 12 hours (max single dose 4g) OR IV/IM: 100mg/kg as a single dose once daily
Gentamicin	IV/IM: 5-7.5 mg/kg as a single dose once a daily

Note: IV=intravenous, IM=intramuscular

Following the 2013 WHO Pocketbook of hospital care for children [27], if the child does not show signs of improvement within 48h of starting intravenous antibiotics and staphylococcal pneumonia is suspected, then the child should switch to gentamicin (dosed as in **Table 6**) and cloxacillin 50 mg/kg IM or IV every 6h. Cloxacillin can be replaced by another anti-staphylococcal antibiotic, for example oxacillin, flucloxacillin or dicloxacillin.

5.2.2 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

The doses of intravenous drugs are as recommended by the WHO pocket book for hospital care 2013 [27] or local standard of care. Intravenous doses may be modified, intervals between doses increased or antibiotics discontinued in the following situations:

- renal failure (all)
- combined renal and liver failure (ceftriaxone)
- therapeutic drug monitoring (gentamicin)

After receiving at least 24h of intravenous antibiotics, children randomised to oral step-down should move to oral antibiotics as soon as they have improved clinically, are currently clinically stable or

continuing to improve and can tolerate oral medication (e.g. without vomiting). See **Section** Error! Reference source not found. below.

5.2.2.A Stopping Drug Early

Adverse events caused by drug toxicity (i.e. adverse reactions) leading to a treatment change are expected to be rare, and should be managed following local standard of care. 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 and follow relevant safety reporting procedures. Children should remain in the study for follow-up and should continue to follow the assessment schedule.

5.2.2.B Inadequate Response or Relapse on Intravenous Treatment or Post-discharge

Non-response to intravenous antibiotics in children randomised to 5 days' intravenous therapy, and subsequent relapse, should be treated as per normal standard of care; example scenarios are provided in **Section 0** below.

5.2.3 Compliance & Adherence

All intravenous doses will be administered by ward nurses and recorded on CRFs\worksheets by study staff. Therefore non-adherence will be minimal.

5.3 ORAL AMOXICILLIN AND CO-AMOXICLAV

5.3.1 Products & Treatment Schedule

Children randomised to oral amoxicillin or co-amoxiclav will be provided with dispersible tablets as trial supplies to be prepared and given orally twice daily by the ward nurses whilst still in hospital and by the parent/carer of the child after discharge, following instructions from the study staff. Medication must be taken as dispersed tablets and not swallowed whole, divided, or crushed. Dosing will be by weight band as shown in **Body weight** should be obtained by ward nurses, using standard methods (as to determine the doses of intravenous antibiotics). Body weight reported by parents is not acceptable. Additionally, body weight should be measured on the day of switch to oral antibiotic to assign the child to the correct weight-band dosing schedule, as weight may change considerably since admission (e.g. if the child was dehydrated at the time of enrolment into the study).

5.3.1.A Criteria for Moving from Intravenous to Oral Antibiotics

The main criteria for moving from intravenous to oral antibiotics is that the child should have improved clinically, be currently clinically stable or continuing to improve, and be well enough to take medication by mouth, i.e. can ingest and keep down the dispersible tablets when made up in a small amount of liquid, and hence oral absorption of the antibiotic is likely to be good. Children may move to oral medication whilst inpatients (e.g. if they are still receiving supplemental oxygen). See MOP for further details.

Children should be discharged on oral medication as soon as they are clinically stable and have received and retained at least one dose of oral antibiotics. See MOP for further details.

Table 7.

Body weight should be obtained by ward nurses, using standard methods (as to determine the doses of intravenous antibiotics). Body weight reported by parents is not acceptable. Additionally, body weight should be measured on the day of switch to oral antibiotic to assign the child to the correct weight-band dosing schedule, as weight may change considerably since admission (e.g. if the child was dehydrated at the time of enrolment into the study).

5.3.1.B Criteria for Moving from Intravenous to Oral Antibiotics

The main criteria for moving from intravenous to oral antibiotics is that the child should have improved clinically, be currently clinically stable or continuing to improve, and be well enough to take medication by mouth, i.e. can ingest and keep down the dispersible tablets when made up in a small amount of liquid, and hence oral absorption of the antibiotic is likely to be good. Children may move to oral medication whilst inpatients (e.g. if they are still receiving supplemental oxygen). See MOP for further details.

Children should be discharged on oral medication as soon as they are clinically stable and have received and retained at least one dose of oral antibiotics. See MOP for further details.

Table 7: Dosing for oral amoxicillin and co-amoxiclav

FORMULATION	WEIGHT BAND	# TABLETS AM	# TABLETS PM	# TABLETS DAILY	DAILY DOSE (MG)
Amoxicillin (250mg tablets)	3 - <6kg	1	1	2	500
	6 - <10kg	2	1	3	750
	10 - <14kg	2	2	4	1000
	14 - <20kg	3	3	6	1500
	20 - <25kg	4	4	8	2100
	25 - <35kg	5	5	10	2500
Co-amoxiclav 7:1 (200/28.5mg tablets)	3 - <6kg	1	1	2	400/57
	6 - <10kg	2	2	4	800/114
	10 - <14kg	3	2	5	1000/142.5
	14 - <20kg	4	4	8	1600/228
	20 - <25kg	5	5	10	2000/285
	25 - <35kg	6	6	12	2400/342
Co-amoxiclav 4:1 (250/62.5mg)	3 - <6kg	1	1	2	500/125
	6 - <10kg	2	1	3	750/187.5
	10 - <14kg	2	2	4	1000/250
	14 - <20kg	3	3	6	1500/375
	20 - <25kg	4	4	8	2000/500
	25 - <35kg	5	5	10	2500/625
Co-amoxiclav 14:1 (150/10.725mg)	3 - <6kg	2	1	3	450/32.175
	6 - <10kg	3	2	5	750/53.625
	10 - <14kg	4	3	7	1050/75.075
	14 - <20kg	5	5	10	1500/107.25
	20 - <25kg	7	6	13	1950/139.425
	25 - <35kg	8	8	16	2400/171.6

Note: inclusion criteria include weights up to 30kg (**Section 3**), but dosing table includes weights up to 35kg to allow for dehydrated children gaining weight during admission, and to align with WHO HIV weight-bands.

5.3.2 DURATION OF ANTIBIOTICS

Children randomised to oral step-down medication will simultaneously be randomised to receive a total antibiotic duration (IV plus oral from start of IV treatment, excluding any (oral/intramuscular) antibiotics taken in the community) of 4 vs 5 vs 6 vs 7 vs 8 days, except for those children in the Phase II PK trial (PediCAP-B) on co-amoxiclav 4:1 or 14:1 who will receive a total of 6 days of antibiotics. Exact numbers of tablets will be prescribed to complete this total duration based on the doses of IVs received, and the child's weight, plus one additional dose in case of lost tablets/vomited dose post-discharge.

See **Section 5.3.4.B** below for management of inadequate response or relapse on oral treatment. Parents/carers of children who are discharged clinically stable with remaining oral medication to complete their randomised course of antibiotics will be instructed to contact the study team if they have any concerns, lose more than one dose, or if the child has persisting symptoms.

5.3.3 Dispensing and Accountability

The investigational medicinal product (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. The IMP will be designated for strict use for trial participants only, and stock will be audited intermittently during the trial at each site.

For all trial drugs, the designated trial pharmacist or nurse will confirm receipt of supplies prior to the commencement of the trial. Inventories will be conducted regularly, and logs returned to the CTU as detailed in the Pharmacy MOP.

Parents/carers will be provided with a full supply of drugs on discharge from hospital, sufficient to complete the randomised total duration of antibiotics exactly plus one additional dose. Parents/carers will be requested to return any unused drug to the clinic at their 4 week visit.

Medication will be provided as tablets to be dissolved in water or other liquid (e.g. breastmilk). The pharmacist, clinician or research nurse will ensure parents/carers understand how the drugs must be given prior to discharge, and parents/carers will be given an information sheet before the child is discharged. This will include clear instructions that tablets must be taken as dispersed tablets and not swallowed whole, divided or crushed.

On no account should any drug assigned to a child be used by anyone else. Unused trial drug must be returned to the site if a child withdraws from treatment before completing their randomised duration of therapy.

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 and returned. The designated pharmacist/nurse will, on receipt of supplies prior to the start of the trial, conduct an inventory and complete a receipt.

Procedures for drug distribution, labelling, accountability and destruction will be detailed in the PediCAP Pharmacy MOP. 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.

5.3.4 Dose Modifications, Interruptions & Discontinuations

Amoxicillin and co-amoxiclav are both active drugs that are routinely given to children with CAP. The doses given to the children in all the study groups are broadly aligned with the internationally recommended amoxicillin dosing range (see **Section 0**).

5.3.4.A Stopping Drug Early

Adverse events caused by drug toxicity leading to a treatment change are expected to be rare, and should be managed following local practice. 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. Children should remain in the study for follow-up and should continue to follow the assessment schedule.

If they happen, severe allergic reactions (immediate type 1 reactions) are expected to occur early while the child in in hospital on a parenteral penicillin-based antibiotic regimen. Severe allergic reactions to either amoxicillin alone or in combination with clavulanate are very rare, but again are expected to occur while the child is in hospital. All parents/carers will be provided with telephone numbers for the study team and be told to return with the child to hospital if there are any acute events. Delayed drug reactions are generally mild and self-limiting and resolve with discontinuation of the drug. The onset of mild delayed reactions is most common 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.

In cases where there is an issue with tolerability of the trial medication resulting in recurrent spitting or gagging, the child should be switched to an alternative amoxicillin or co-amoxiclav formulation where available locally, or to another antibiotic if not available locally and 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. Requirement to switch from the IMP to an alternative formulation of amoxicillin or co-amoxiclav for these reasons will be reported on CRFs\worksheets for the reason of tolerability. All such children will continue follow-up in the trial, “off-study-drug, on-study” (see **Section 5.7** below).

5.3.4.B Inadequate Response or Relapse on Oral Treatment or Post-discharge

The management of potential inadequate response to the randomised antibiotic regimen and/or relapse after the completion of therapy as prescribed will be based on a range of potential scenarios. These will be fully described in the MOP, but example scenarios are included in **Section 0** below.

5.3.5 Compliance & Adherence

Amoxicillin and co-amoxiclav are widely used worldwide for treatment of bacterial respiratory tract infections, with extremely low rates of toxicity. Mild unwanted side-effects, including diarrhoea and thrush, have been reported [48, 49], and these will be directly solicited. 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 and tolerability will be assessed during the week 1 (and week 2 if appropriate) telephone follow-up.

Amoxicillin suspension is the most commonly used single antibiotic formulation for the treatment of children globally [50]. In this study, older (and heavier) children will receive a relatively large number of tablets per single dose, but dispersed this should still be less volume than oral solution. The twice daily dosing schedule used is known to make administration of antibiotics to schedule easier for parents and improve compliance [51].

Adherence to the prescribed course, and tolerability of the dispersible tablets, will be assessed by adherence questions in telephone clinical assessments post discharge from hospital. The importance of adherence should be reinforced prior to discharge from hospital, and during telephone calls.

5.4 INADEQUATE RESPONSE TO TREATMENT

The management of potential inadequate response to intravenous antibiotics or the randomised antibiotic regimen and/or relapse after the completion of therapy as prescribed will be based on a

range of potential scenarios. These will be fully described in the MOP, but example scenarios are included in **Table 8** below.

Table 8: Example scenarios of inadequate response or relapse

TIMING	SCENARIO	ACTION*
DURING PRIMARY HOSPITAL ADMISSION OR WITHIN ORIGINALLY RANDOMISED TREATMENT COURSE		
Any time	Child clinically deteriorates, e.g. with severe respiratory distress or septic shock	Chest X-ray is strongly recommended. Treat with injectable antibiotics as per normal standards of care (e.g. moving to second line treatment regimen according to local standard of care).
	Positive blood culture or other test result suggesting more serious manifestation of severe CAP	Manage according to local standard of care (e.g. moving to different intravenous antibiotics, treating for longer than original randomisation depending on clinical status of the child).
After two days IV	No improvement in clinical status on IV therapy	Manage according to local standard of care (e.g. moving to cloxacillin if staphylococcal pneumonia is suspected, or to second-line, or repeating laboratory tests where available). Consider TB.
After oral switch	Child has persistent symptoms and signs of a respiratory tract infection after oral switch, e.g. with continued fever, tachypnoea, tachycardia, but remains clinically stable. Appears to be tolerating oral medication.	Continue oral medication as randomised: most likely infection is viral. Also consider evaluation for TB.
	Child has persistent symptoms and signs of a respiratory tract infection and is NOT tolerating oral medication due to severe persistent vomiting or diarrhoea	Switch to IV or injectable antibiotics as per normal standards of care.
AFTER DISCHARGE FROM PRIMARY ADMISSION OR AFTER COMPLETION OF INITIAL RANDOMISED COURSE		
Any time	Child has persistent symptoms of a mild respiratory tract infection, with no signs of pneumonia	No treatment for CAP. A child with persistent cough and fever for more than 2 weeks and signs of pneumonia after adequate antibiotic treatment should be evaluated for TB.
	Child has signs of pneumonia, and fulfils the diagnostic criteria of non-severe CAP	Treat as per normal standards of care. Consider TB.
	Child has signs of pneumonia, and fulfils the diagnostic criteria of severe CAP	Admit. Chest X-ray is strongly recommended. Treat with IV or injectable antibiotics as per normal standards of care. Consider TB.

* Regardless of action taken, children will continue to be followed up "on study-off study medication" until 28 days post-randomisation. See **Section 0**.

5.5 HANDLING CASES OF TRIAL MEDICATION OVERDOSE

Parents/carers of the children participating in the study should be counselled about the importance of taking the oral medications as prescribed. Although renal injury has been described in children after accidental amoxicillin overdose, this is rare even in single doses above 250mg/kg [44], which is much higher than the highest daily dose in PediCAP of 167 mg/kg/day. Parents/carers should contact the PediCAP team immediately if their child has been overdosed, to receive appropriate advice. Children will then be managed on a case by case basis, and toxicity will be managed in all randomised groups according to standard clinical practice. Instances of overdose with IMP will be deemed as a deviation from study procedure and a notable event (**Section 0**) and will be reported as such.

5.6 UNBLINDING / UNMASKING

PediCAP is an open label trial so unblinding/unmasking will not be necessary.

5.7 PROTOCOL TREATMENT DISCONTINUATION

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

- Inadequate response or relapse on trial treatment
- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the child's condition that justifies the discontinuation of trial treatment in the clinician's opinion
- Use of a medication that is essential for the child's management with a known major or moderate drug interaction with the trial antibiotics
- Inadequate compliance with the protocol treatment in the judgement of the treating physician, including for reasons of tolerability, see **Section 5.3.4.A** above
- Overdose with trial drug
- Withdrawal of consent for treatment by the child or parent/carer

As the child's participation in the trial is entirely voluntary, they or their parents/carers may choose to discontinue the trial treatment **at any time without penalty or loss of benefits to which they are otherwise entitled**. The parent/carer/child **is not required to give a reason for discontinuing their child's trial treatment**; however, if possible, a reasonable effort should be made to establish this reason while fully respecting the child and family's rights.

Children stopping randomised trial treatment should remain in the trial for the purpose of follow-up and data analysis "on-study, off-study-treatment" (unless the parent/carer explicitly withdraws their consent from all stages of the trial) to contribute to the "intention-to-treat" analysis. Any other non-trial medication a trial child receives will be recorded on CRFs\worksheets. If a child is withdrawn from all follow-up, refer to **Section 6.6**.

Data will be kept and included for children who stop follow-up early.

5.8 TREATMENT DATA COLLECTION

Information about all antibiotics and concomitant medication received, including formulation, frequency, dose and reasons for change will be collected on the CRF\worksheet.

5.9 NON-TRIAL TREATMENT

All oral, intravenous, intramuscular and topical treatments for any condition are considered a concomitant medication, including blood transfusion.

5.9.1 MEDICATIONS PERMITTED

All necessary concomitant medications are allowed. Regular medications will be recorded at baseline. Parents will be asked to report the use of additional medications during follow-up telephone calls, including traditional medicines. If a medication with a known major or moderate drug interaction with amoxicillin (see **Section 5.9.2**) 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**).

5.9.2 MEDICATIONS NOT PERMITTED

Medications with known interactions with amoxicillin, which include allopurinol, methotrexate and mycophenolate, 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 vaccines. These immunisations, if included in the immunisation schedules of participating sites, should be postponed until after completion of trial medication.

5.9.3 TREATMENT AFTER TRIAL EVENT

Treatment will be at the discretion of the responsible physician.

5.10 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.3**.

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 **Table 1** and **Figure 1Error! Reference source not found.**).

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, even if their trial medication is discontinued prematurely (see **Section 0**). The target dates for trial 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:

- Trial entry (day 1): Baseline information will be collected, and a face-to-face assessment will be made
- Daily until discharge: face-to-face assessment will be made
- Day of discharge: face-to-face assessment and confirmation of contact details
- Week 1, 2, & 3: follow-up telephone call (or face-to-face if usual practice)
- Week 4: face-to-face follow-up (in exceptional circumstances, this visit may be conducted by telephone if the child is unable to attend the clinic/hospital)
- Acute events: face-to-face assessment if child returns to the randomising site

6.1.1 BASELINE INFORMATION

At randomisation, medical and relevant social history, including demographics and socioeconomics, documentation of any underlying diseases, mode of delivery, documentation of immunisation status (including taking copies of immunisation records where available), duration of symptoms to date and recent antibiotic exposure, will be recorded. Locator information, including physical address and contact phone numbers will also be collected. Anthropometry will include weight, height/length and mid-upper arm circumference (MUAC) (height/length and MUAC may be collected as soon as practicable post-baseline if not possible to assess at trial entry). Vital signs (respiratory and heart rate, oxygen saturation) and temperature will be measured. Relevant respiratory symptoms and signs will be solicited. Chest X-rays at randomisation will be strongly encouraged where site facilities allow, but are not mandatory. Where possible, and where available, digital copies of all chest X-ray images will be collected.

6.1.2 FACE-TO-FACE ASSESSMENT

A physical examination must be performed at each face-to-face assessment, including acute events if the child returns to the randomising site.

The following will be recorded for all face-to-face assessments:

- Vital signs (respiratory and heart rate, oxygen saturation) and temperature (during hospitalisation only)
- Symptoms and clinical signs, specific solicited side-effects and adverse events
- Concomitant care/healthcare utilisation
- Results of any haematology/biochemistry/microbiological investigations/chest X-rays undertaken as part of the usual standard of care, but not required by the trial

Children will be weighed on the day of step-down to oral antibiotics to ensure correct dosing and at the week 4 face to face visit.

If the child is in hospital at the week 4 visit (either still admitted from randomisation, or re-admitted), the total duration of that hospitalisation and resource use during it will be collected through to discharge (even though follow-up formally finishes 28 days after randomisation).

If the parent/carer did not bring the child's immunisation record at their original admission, they will be asked to bring it to the week 4 face to face visit, where it will be copied.

6.1.3 DAY OF DISCHARGE

At discharge, locator information collected at baseline will be verified together with two telephone numbers (wherever possible) which should both be called whilst the parents/carers are present to confirm that correct information has been provided. Tolerability of oral medication will be assessed in children who have stepped down to oral.

6.1.4 WEEKS 1, 2 & 3

Telephone contact will be made by sites to parents/carers of children who are not still in hospital at week 1, week 2 and week 3 (see **Table 1** for visit windows). Contact will be face-to-face if the child has not been discharged from hospital, or if this is part of normal standard of care at the site.

Sites may choose to re-schedule 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 (**Table 1, Figure 2**).

6.1.4.A Telephone Contact

A review of clinical signs and symptoms must be performed at each telephone contact during follow-up. At a minimum, 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 or co-amoxiclav.
- Solicited clinical adverse events since last protocol contact, including rashes, diarrhoea, vomiting, gastrointestinal events, and thrush/candida.
- Any acute illnesses requiring assessment by a healthcare provider (including traditional healers) since last protocol contact, including whether any antibiotic prescriptions were issued.
- Systemic antibiotic treatment since last protocol contact, including, as appropriate, adherence to PediCAP treatment and whether any additional/new antibiotic prescriptions were issued.
- Adherence and tolerability of PediCAP treatment, including any medication errors (week 1 only).
- Concomitant care/healthcare utilisation (including traditional healers).

6.1.5 ACUTE EVENTS

Parents/carers will be given a card with the contact details for the trial research team at their site, and encouraged to return to the site if the child becomes acutely unwell during the follow-up period. During any acute events, the child can be seen face-to-face if attending the randomising site. Otherwise, telephone contact can be arranged.

6.2 CHILDREN UNDERGOING PK SAMPLING

A total of 180 children will undergo PK sampling. This will consist of 60 children in the main trial (PediCAP-A) randomised to co-amoxiclav and receiving the standard co-amoxiclav 7:1 ratio (independently of total duration of antibiotic therapy randomisation). A further 120 children will be randomised to oral step-down with co-amoxiclav 4:1 versus 14:1 ratios (60 in each group) in a Phase II PK trial (PediCAP-B). The assessment schedule for these 120 additional children will be the same as for children in the main trial. For all patients undergoing PK sampling, additional informed consent will be sought for taking PK samples. Children will have up to 5 PK samples taken immediately before and then over up to 12h after their first morning dose. See **Section 10.1** for more details.

6.3 CHILDREN UNDERGOING MICROBIOLOGICAL SAMPLING

66 children per site recruited with parental consent will undergo microbiological sampling (total n=330).

The assessment schedule for children with microbiological sampling will be:

- **Trial entry:** parents will be asked for additional informed consent for their child to undergo microbiological sampling. Children will have nasopharyngeal and peri-rectal swabs taken at baseline to assay carriage of commensal organisms and antimicrobial resistance genes. Collection should be as soon as possible after initiation of intravenous antibiotics. If a child is wearing a nappy, or passes a stool, a sample of faecal material may be taken instead of a peri-rectal swab.
- **Day of discharge:** Children will have a repeat peri-rectal swab (or nappy/faecal sample as above) taken to test for acquisition of antibiotic resistant genes during hospitalisation. Half the children in the microbiology substudy will also have a nasopharyngeal swab taken at this timepoint (determined by an additional randomisation, to the second nasopharyngeal swab being taken at discharge or week 4).
- **Week 4 face-to-face follow-up:** Children will have a peri-rectal swab (or nappy/faecal sample as above) taken to assay for the total effects of hospitalisation and antibiotic treatment on carriage of commensal organisms and antimicrobial resistance genes. Half the children in the microbiology substudy will also have a nasopharyngeal swab taken at this timepoint (as determined by the additional randomisation; therefore each child will have two nasopharyngeal swabs in total, one at trial entry and one at discharge or week 4).

6.4 MICROBIOLOGICAL TESTS

A summary of the sample collection requirements are provided below; please refer to the PediCAP sample collection MOP for details.

6.2.1 NASOPHARYNGEAL SWABS

Fine bore nasopharyngeal swabs will be collected to assess the impact of the different antibiotic regimens and durations on antimicrobial resistance in the nasopharyngeal commensal flora. Samples will be frozen and shipped in batches to Antwerp for processing.

6.2.3 PERI-RECTAL SWABS

Peri-rectal swabs will be collected to allow for the evaluation of the impact of antibiotic and hospital exposure on antibiotic resistance in the gastrointestinal commensal flora. If a child is wearing a

nappy, or passes a stool, a sample of faecal material may be taken instead of a peri-rectal swab. Peri-rectal swabs are minimally invasive, can be taken in a standardised manner independent of passing stools using a soft swab and very soon after enrolment, minimizing antibiotic pre-exposure. They have been successfully used in other antibiotic trials in sub-Saharan Africa investigating impact of antibiotic exposure on the gastrointestinal commensal flora in a similar age group as PediCAP (personal communication, e.g. FLACSAM trial, ClinicalTrials.gov Identifier: NCT03174236), and were found to be highly acceptable to families.

6.5 LABORATORY AND RADIOLOGICAL TESTS

Point-of-care semi-quantitative C-reactive protein testing will be carried out as part of screening for PediCAP based on a separate screening informed consent, using standardised kits provided by the trial. Blood samples for this can be obtained as part of routine blood sampling, if carried out, or from a finger or heel prick.

There are no other mandatory laboratory assessments and no mandatory radiological assessments for children recruited into PediCAP. However, results of the following should be recorded, if carried out as part of routine clinical care:

- Haematology: haemoglobin; platelets; white cell count; neutrophil, lymphocyte and eosinophil counts
- Biochemistry: CRP or other inflammatory markers (e.g. procalcitonin), urea, creatinine and electrolytes
- Microbiology: any organism isolated from any specimen (e.g. blood, sputum, urine, cerebrospinal fluid, pleural fluid) together with any antimicrobial susceptibilities
- Virology: rapid testing for RSV, Influenza A/B of other respiratory viruses (any method)
- Radiology: chest X-ray radiological report (where available electronically, digital copies will be archived for the trial)

6.6 PROCEDURES FOR ASSESSING EFFICACY

The primary measure of efficacy in PediCAP is re-admission to hospital or death within 28 days of randomisation. This will be ascertained through solicited questions at follow-up visits/calls. Both outcomes are also serious adverse events (SAEs), and reportable as such. Parents/carers will be encouraged to return to the trial site if their child becomes acutely unwell during trial follow-up. An endpoint review committee with a majority of independent members will review all deaths and readmissions to adjudicate whether they are related to pneumonia (a secondary endpoint).

Other efficacy measures include length-of-stay and duration of oxygen supplementation for the initial admission, which will be determined from regular in-hospital follow-up and the medical notes. A symptom checklist will be used at each telephone visit by a nurse to solicit clinical symptoms.

All antibiotics received during the primary admission will be recorded on the CRFs\worksheets, together with the reasons for any changes. Information about all post-discharge antibiotic prescriptions will be elicited at each scheduled contact with the trial team during the follow-up period. 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 CRFs\worksheets.

6.7 PROCEDURES FOR ASSESSING SAFETY

The clinical examination at each face-to-face contact and follow-up telephone calls will explicitly prompt for symptoms relating to possible drug toxicities. Additional safety blood tests or investigations may be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated following routine clinical practice. Results of any laboratory tests conducted as part of routine clinical practice will be recorded on CRFs\worksheets.

Adverse events (clinical and laboratory) will be graded using the 2017 Division of AIDS (DAIDS) toxicity grading scale v2.1 (see **Appendix I**), with a minor modification of the neutrophil count grading to reflect norms in the African populations. All adverse events of any grade that lead to modification of antibiotics or are considered related to antibiotics will be reported on CRFs\worksheets, as will any Grade 3 or 4 adverse events and SAEs. Other adverse events will be recorded in the clinical notes but will not be reported on CRFs\worksheets – the reason is that grade 1 and 2 adverse events will be very common as the children will be sick when admitted. They will therefore not be informative as they commonly reflect the underlying disease process rather than any impact of the medication. SAEs (and other notable events) will be defined according to ICH GCP, and should be reported to the CTU within 1 working day of the site being aware (see **Section 7**). All adverse events meeting these SAE definitions should be reported on study CRFs\worksheets, regardless of their relationship to pneumonia.

Telephone follow-up calls will explicitly prompt for known clinical adverse effects of amoxicillin and co-amoxiclav, primarily gastrointestinal symptoms including diarrhoea, vomiting, rash and thrush/candida. Additional investigations may be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Pre-specified clinical complications including sepsis, lung abscess, empyema, and line complications will be recorded on the CRF\worksheet.

6.8 OTHER ASSESSMENTS

6.8.1 HEALTH ECONOMICS AND RESOURCE UTILISATION (ALL CHILDREN)

Policymakers require information on the costs, health effects and equity implications of alternative interventions when considering how to allocate limited resources to meet the population's health needs. We will estimate costs and cost-effectiveness of the trial's treatment strategies evaluated using generic health measures (e.g. disability-adjusted life-years (DALYs)-averted) to allow for comparison with other interventions. Resource use and total costs will be estimated using trial data and other sources (e.g. unit costs/prices) to be representative of African countries in general. The cost-effectiveness of more effective but more expensive alternatives will depend upon whether the health gains offered are large enough compared to other calls on limited country budgets to be deemed "value-for-money", so we will outline criteria upon which this assessment can be made.

The trial will measure healthcare-related costs in trial children, starting at randomisation and continuing for the duration of follow-up. Costs incurred by the children and their families (transport, indirect and companion person's costs) will be obtained by caregiver reports, and be recorded in CRFs\worksheets. Family information (e.g. parental age, educational level and broad measures of socio-economic status) will be recorded on CRFs\worksheets at baseline. Household level cost data will be collected through a brief follow-up survey. Reported transport costs will be confirmed using local information on distance and cost of transport.

For the cost-effectiveness analysis, we will calculate an average cost per child treated. From the provider's perspective, this cost will include patient-specific resources (medications, investigations, products, oxygen, procedures etc) in addition to overhead and staff costs incurred during each admission.

The patient-specific resources will be extracted from CRFs\worksheets, and will include intravenous antibiotics, oral antibiotics, any blood or urine tests done as part of routine care (none mandated by the trial), supplemental oxygen, intravenous fluids, radiology or additional procedures (for instance insertion of a chest drain for a pleural effusion). The price/cost/charge for each of these resources will be sourced from trial sites and from trial financial data.

Overhead and staff costs will be sourced from routine hospital expenditure data. Overheads include running costs such as electricity, water, cleaning, laundry, security, administration and maintenance costs. In addition, routine hospital expenditure data will provide an estimate of the hospital expenditure on staff (anonymised). Overhead and staff costs will be allocated to an inpatient day using the patient day equivalent method in order to estimate an overhead and staff cost per inpatient day or per admission. The patient day equivalent for each site will be estimated from routine hospital statistics such as number of inpatient days and number of outpatient or emergency department visits.

6.9 EARLY STOPPING OF FOLLOW-UP

The trial will distinguish between stopping of trial treatment and stopping of trial follow-up. Whilst stopping trial follow-up requires stopping trial treatment if the child is still receiving antibiotics as randomised, stopping trial treatment does not necessarily mean that the child automatically has to stop trial follow-up. **The parent/carers wishes with respect to trial treatment and trial follow-up should be respected at all times.** If a parent/carer who chooses to discontinue trial treatment for their child remains happy to follow the other trial procedures and follow-up schedule, their child may remain in the trial **"on-study, off-study-treatment"**. However, if they do not wish to remain on trial follow-up, their decision must be respected and the child will be withdrawn from trial follow-up. The CTU should be informed of this in writing using the appropriate documentation. Prior to transferring to routine follow-up, the parent/carer will be asked whether they would be happy for their child to have assessments performed as for the final study visit. They would be at liberty to refuse any or all individual components of the follow-up assessments and their wishes should be respected.

If follow-up is stopped early, the anonymised medical data collected during their participation in the trial will be kept and used in the analysis; consent cannot be withdrawn for the use of historical anonymised data already collected. Consent may be withdrawn at the discretion of the parent/carer for the future use of any stored samples.

Given the short follow-up period (28 days), children who have left the trial may not re-consent to participation in the trial at a subsequent hospitalisation episode.

Children who stop trial follow-up early will not be replaced, since the sample size calculation already incorporates an inflation factor to account for lost-to-follow-up.

6.10 LOSS TO FOLLOW-UP

Follow-up is only for 28 days, and therefore we anticipate a low rate of lost-to-follow-up. We plan to telephone parents/carers after 1, 2 and 3 weeks post-randomisation (when this occurs post-discharge) to ensure that contact is maintained before the face-to-face follow-up at week 4. The patient information sheets will be clear that maintaining contact for 28 days is a necessary part of inclusion in the trial, and parents/carers will be compensated for travel to the follow-up visit in accordance with existing recommendations by local ethics committees.

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

6.11 COMPLETION OF PROTOCOL FOLLOW-UP

The trial will end after the last scheduled 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. **Section 7.1** lists definitions, **Section 7.3** gives details of the investigator responsibilities and **Section 7.4** provides information on CTU responsibilities.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in **Table 9**.

Table 9: Adverse events 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, as set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	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 ▪ Consists of a congenital anomaly or birth defect ▪ 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 child 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 (IMP) and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision). For PediCAP this includes oral amoxicillin, oral co-amoxiclav and the IV antibiotics listed in Table 6.

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP antibiotic should be reported appropriately from the point of signing main consent.

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 ADVERSE EVENTS

Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g. elective cosmetic surgery, social admissions
- Overdose of medication without signs or symptoms

7.2 OTHER NOTABLE EVENTS

Notable events are overdose, abuse or misuse of IMP.

Misuse of a medicinal product is defined as situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

Abuse of a medicinal product is defined as persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

There are no other notable events.

The CTU should be notified of all notable events within 1 working day of the investigator becoming aware of the event, using the SAE/Other Notable Event Form (see **Sections 7.3.1.E** and **7.3.2**).

7.3 INVESTIGATOR RESPONSIBILITIES

7.3.1 INVESTIGATOR ASSESSMENT

7.3.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the child must first assess whether or not the event is serious using the definition given in **Table 9**. If the event is serious, then an SAE/Other Notable Event Form must be completed and the CTU notified within 1 working day.

7.3.1.B Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the 2017 Division of AIDS (DAIDS) toxicity grading scale v2.1 in **Appendix I**, with a minor modification of the neutrophil count grading to reflect norms in the African population.

7.3.1.C Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy, as related or unrelated, using the definitions in **Table 10**. The level of certainty supporting the two categories of related vs unrelated can vary: **Table 10** shows how the five categories of the Naranjo classification (unrelated, unlikely, possible, probable, and definitely related to receipt of the study drug) map onto the related/unrelated categories. If the causality assessment is unrelated or unlikely to be related, the event is classified as an unrelated SAE. If the causality is assessed as possible, probable or definitely related, the event is classified as an SAR.

Table 10: Assigning Type of SAE Through Causality

SAE TYPE	FURTHER DETAILS OF RELATIONSHIP	DESCRIPTION
SAR (related)	Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
SAR (related)	Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
SAR (related)	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 child's clinical condition, other concomitant treatments).
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 child's clinical condition, other concomitant treatment).
Unrelated SAE	Unrelated	There is no evidence of any causal relationship

7.3.1.D Expectedness

The Sponsor has the final responsibility for determination of expectedness in the trial. 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 9**. If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.3.1.E Notification

The CTU should be notified of all SAEs and other notable events within 1 working day of the investigator becoming aware of the event using the SAE/Other Notable Event Form.

Investigators should notify the CTU of all SAEs and other notable events occurring from the time of signature of the main informed consent form until the child exits the trial.

All adverse events of any grade that lead to modification of antibiotics or are considered related to antibiotics will be reported on CRFs\worksheets, as will any Grade 3 or 4 adverse events and SAEs. Other adverse events will be recorded in the clinical notes but will not be reported on CRFs\worksheets.

7.3.2 Notification Procedure

1. The SAE/Other Notable Event Form must be completed by an investigator (the physician named on the Signature List and Delegation of Responsibilities Log, who is responsible for the child's care; this will be either the Principal Investigator or another medically qualified person with delegated authority for SAE reporting). Due care should be paid to the grading and causality 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 emailed as appropriate. The responsible investigator should subsequently check the SAE/Other Notable Event Form, make changes as appropriate, sign and then re-send to the CTU 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 Study ID, name of investigator reporting the event, and why it is considered serious.

2. The SAE/Other Notable Event Form must be sent by email to mrcctu.pedicap@ucl.ac.uk within 1 working day of becoming aware of the event.

3. Follow-up: 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/Other Notable Event Form, indicated as 'Follow-up' should be completed and emailed to the CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The child must be identified by Study ID only. The child's name should not be used on any correspondence and should be deleted from any test results.

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

SERIOUS ADVERSE EVENT (SAE) AND OTHER NOTABLE EVENT REPORTING
Within 1 working day of becoming aware of an SAE/other notable event, please email a completed SAE/Other Notable Event Form to the MRC CTU at UCL on mrcctu.pedicap@ucl.ac.uk

7.4 MRC CTU RESPONSIBILITIES

Medically-qualified staff at the MRC CTU and/or the Chief Investigator (or a medically-qualified delegate) will review all SAE reports received. The causality assessment given by the local investigator at the site cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports. The medical reviewer will assign expectedness.

The MRC CTU is undertaking the duties of the trial Sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committees, as appropriate. This responsibility is delegated to country PIs for relevant reporting requirements in individual countries.

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

Pharmaceutical companies will also be notified of all reportable events according to the agreed contractual arrangements.

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 CTU's Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), Safety Reporting Plan and Monitoring Plan which will be separately reviewed by the Quality Management Advisory Group (QMAG).

8.2 CENTRAL MONITORING AT CTU

Each site will be responsible for its own data entry and local trial management. Data will be entered into the online trial database directly at the site. The site will retain the original CRFs\worksheets. Data stored on the central database will be checked at CTU for missing or unusual values (range checks) and checked for consistency within children over time. If any problems relating to data quality are identified, the site will be contacted and asked to verify or correct the entry. Changes will be made on the original CRF\worksheet and entered into the database at the site. CTU will also send reminders for any overdue and/or missing data with the regular inconsistency reports of errors.

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

Staff from MRC CTU at UCL will visit clinical sites to validate and monitor data, and independent local monitors will be employed in each country to make regular visits to trial sites. 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.

A detailed site initiation visit with training will be performed at each study site by staff from the CTU. The site initiation visits will include training in the administration and side effects of study drugs, as well as the trial procedures.

Monitoring and site training will be carried out at least twice a year at each site by CTU staff or Africa-based monitors. The monitoring will adhere to the principles of GCP. The CRFs\worksheets of 5-10 children enrolled will be reviewed at the first monitoring visit. A sample of no less than 5 children will be selected by CTU for review at subsequent visits. Priority will be given to selecting children for whom the CRFs\worksheets have not been previously monitored.

Monitors will:

- verify completeness of the Investigator Site File
- confirm adherence to protocol

- review eligibility verification and consent procedures
- look for missed clinical event reporting
- verify completeness, consistency and accuracy of data being entered on CRFs\worksheets
- verify completeness, consistency and accuracy of PK study data and samples
- evaluate drug accountability
- provide additional training as needed

The monitors will require access to all patient medical records including, but not limited to, laboratory test results and prescriptions. The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved.

8.3.1 Direct Access to Children's 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. Parental/caregiver consent must be obtained for this. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should all be verifiable from source documents:

- signed consent forms
- dates of visits including dates any trial specimens were taken and processed in the laboratory
- eligibility and baseline values for all children
- child clinical and laboratory data
- clinical endpoints
- serious adverse events, adverse events and notable events
- dates drug dispensed and (if necessary) drugs returned
- pharmacy/clinic drug logs
- concomitant medication dispensed

Not all such information will be monitored; rather the monitoring plan will describe a risk-based approach to monitoring based on ongoing random samples of patient clinical and laboratory data, which may be increased if issues are identified.

8.3.2 Confidentiality

We plan to follow the principles of the EU General Data Protection Regulation 2016/679 and the UK Data Protection Act regardless of the countries where the trial is being conducted. In particular, the investigator must ensure that children's anonymity will be maintained and that their identities are protected from unauthorised parties. Children will be assigned a trial identification number and this will be used on CRFs\worksheets; children will not be identified by name. The investigator will keep securely a patient trial register showing Study IDs, name, initials and date of birth, held only at the local site. The unique Study ID (or laboratory tracking number) will identify all laboratory specimens, CRFs\worksheets, and other records and no names will be used on forms or samples, in order to maintain confidentiality. Copies of the child's immunisation records will be taken to provide an objective assessment of immunisations received (rather than relying on self-report), but names and any other personal identifiers (eg hospital number) will be blocked out before copies are taken. All records will be kept in locked locations. Clinical information will not be released without written permission, except as necessary for monitoring by the trial monitors.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Randomisation will be stratified by site (5 sites, each recruiting 220 children). This factor has been chosen because of practicality (see below) and because it has the potential to modify treatment effects (i.e. lead to interaction) due to variation in other clinical management across sites, meaning forcing balance across the randomised groups is most important for this factor. Sites also vary in local standard of care of their most commonly used backbone IV antibiotics (allowed by the trial, see inclusion criteria in **Section 3**). All other factors should be balanced between groups by the randomisation. The other randomisation in the factorial design is also effectively a stratifier, and hence ensures balance for each randomisation with respect to the other – effectively each child is randomised to one of eleven groups (oral drug × duration (10 groups) plus continuous IV). If instead there were two separate randomisation lists for the oral drug and the total antibiotic duration, then by chance randomised groups for the former could be imbalanced with regard to the latter randomisation (and vice versa).

Randomisation lists will be prepared by staff at CTU under the direction of the Trial Statistician using random permuted blocks with variable size, stratified by clinical site. See **Section 4.1** for details of randomisation practicalities.

9.2 OUTCOME MEASURES

9.2.1 PRIMARY OUTCOME MEASURE

The primary outcome measure is:

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

9.2.2 SECONDARY OUTCOME MEASURES

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

- Proportion of children experiencing CAP-related readmission to hospital or CAP-related death within 28 days post-randomisation (CAP-relatedness adjudicated by the independent Endpoint Review Committee)
- Length of stay required during the index hospitalisation (days) (excluding any additional day remaining in hospital solely for the purpose of trial-related pharmacokinetic studies, see **Section 10.1**), and total days of stay in hospital up to 28 days
- Proportion of children dying within 28 days post-randomisation (all-cause mortality)
- Total days of supplemental oxygen during index hospitalisation
- Total days of antibiotic exposure during 28 days post-randomisation, including antibiotics received during the initial hospitalisation and antibiotics self-reported by parents/carers at follow-up visits
- Proportion of children requiring modification of randomised antibiotics for any reason other than early stopping, or requiring a subsequent course of antibiotics for any reason up to 28 days (also considered as separate components)
- Proportion of children requiring modification of randomised antibiotics for inadequate response, or additional courses in the index hospitalisation for CAP relapse

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

- Experiencing SAEs, including hospital-acquired infections

- Experiencing grade 3 or 4 adverse events
- Experiencing antibiotic-related adverse events
- Experiencing key solicited events (reflecting common drug toxicities), specifically diarrhoea, vomiting and gastrointestinal disorders, skin rashes, thrush/candida
- Modifying antibiotics for antibiotic-related adverse events (i.e. toxicity)
- Experiencing specified clinical complications including sepsis, lung abscess, empyema
- Experiencing line complications (complications related to IV access)

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

9.2.3 Other Outcome Measures

Other outcomes include:

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

Antimicrobial resistance outcomes are:

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

Costs and cost-effectiveness will also be evaluated (see **Section 0**), as will pharmacokinetics of amoxicillin and co-amoxiclav (see **Section 10.1**).

9.2.4 Protection from Bias

It is not practical to use placebos for the multi-drug multi-duration regimens used in this trial, given the relatively large differences in numbers of tablets across the different weight-bands. Further the co-amoxiclav and amoxicillin tablets are different meaning a “double dummy” approach would be needed (each child receives either active co-amoxiclav and placebo amoxicillin or placebo co-amoxiclav and active amoxicillin). Introduction of placebo would therefore increase the pill burden substantially and will be logistically infeasible. It is also not ethical to give children sham IV treatment, which would also defeat one of the key purposes of the trial which is to investigate oral step-down as a mechanism to reduce length of hospitalisation.

Therefore, to counter the possibility of bias, objective outcome measures have been chosen as much as possible. The primary endpoint is re-admission to hospital or death within 28 days post-randomisation. Hospital admissions are clinically significant events and it is reasonable to assume, therefore, that they will be approximately ascertained without bias. The trial will pay for visits to the hospital, if required, within the follow-up period (where healthcare is not free of charge), meaning that parents/carers will have a reason to come back to the original hospital rather than go elsewhere. Every effort will be made to minimize losses to follow-up and to ascertain outcomes completely, thus avoiding bias from differential ascertainment between the randomised groups. Any child lost-to-follow-up will be traced for vital status based on location and mobile phone data verified before discharge (with consent for this). To further protect from bias, an independent Endpoint Review Committee will adjudicate on the causes of death and of hospitalisation (to enable an unbiased assessment of the secondary outcome, CAP-related readmission/death) and whether (without knowledge of actual randomisation) events were unlikely, possibly/probably or uncertainly to have been related to each intervention, were those affected to have received them. This will increase the objectivity of these assessments and increase consistency between sites.

Following recommendations in adults [52], we have avoided using a "test of cure" approach to define endpoints precisely because of substantial challenges in its unbiased assessment outside a placebo-controlled trial. In paediatric CAP, particularly in very young children, symptom recovery scores are also highly subjective and therefore we have not considered these as primary or secondary endpoints either.

Secondary outcomes include length of stay; hospitalisations will be paid for by the trial (if not free of charge) so there will be no pressure to discharge children differentially between randomised groups. Other secondary outcomes include change in antibiotics: the trial protocol (**Table 8**) and manual of operations will contain criteria supporting failure of antibiotic therapy and need to switch, promoting consistency in antibiotic management regardless of original randomisation and minimizing bias. The trial is, however, designed to be pragmatic and reflect what would happen in the real-world where, for example, WHO guidelines were to recommend stepping down to oral therapy for 4 days total duration; in that some children would still need to switch antibiotics and others continue beyond 4 days. What the trial will provide is estimates of these proportions and overall effects on outcomes.

9.3 SAMPLE SIZE

9.3.1 MAIN TRIAL (PEDICAP-A)

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

Randomizing 500 children between 5 equidistant duration groups for amoxicillin and for co-amoxiclav is sufficient to estimate the duration response curve within a 5% error margin in >95% of simulations [33].

For comparison of the co-amoxiclav step-down with the 5-day intravenous groups, randomising 500 vs 100 children respectively provides 89% power to demonstrate non-inferiority based on a 10% non-inferiority margin for a 9% failure rate (two-sided alpha=0.05) (power is >80% for failure rates up to 12%). A 10% non-inferiority margin has been recommended by the United States (US) Food and Drug Administration (FDA) for adult bacterial CAP based on similar hypothesised event rates with and without antibiotics to those observed in children [53].

Therefore the total sample size for the main trial (PediCAP-A) is 1,100 (including the additional 5-day intravenous group). There is no formal adjustment for non-compliance because the trial is pragmatic, designed to evaluate the impact of strategic approaches to antibiotic choice and duration. Rather, non-compliance is a separate secondary outcome (incorporating change from allocated antibiotic regimen for any reason) which will be analysed separately, and the results of the primary analysis interpreted conditional on this.

9.3.2 PHASE II PK TRIAL (PEDICAP-B)

See **Section 10.1**.

9.4 INTERIM MONITORING & ANALYSES

A Data Monitoring Committee (DMC) Charter will be drawn up that describes the membership of the DMC, relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses. The Charter will also contain a description of stopping guidelines: at minimum, these will contain a recommendation for early stopping of the minimum duration group if there is evidence beyond reasonable doubt (Haybittle-Peto stopping rule) that the minimum duration is inferior to the maximum duration on the primary endpoint, with a similar stopping guideline for the comparison of the two oral formulations.

The DMC will meet within 6 months after the trial opens; although the DMC will in general meet annually, the frequency of subsequent meetings will be determined by the DMC and could be more frequent if deemed necessary. The DMC can recommend premature closure or reporting of the trial, or that recruitment to any randomised group be discontinued or modified. Such recommendations would be made if, in the view of the DMC, there is proof beyond reasonable doubt that one of the allocated strategies is better than its comparator in terms of a difference of clinically significant magnitude in a primary outcome.

The guiding statistical criteria for "proof beyond reasonable doubt" is a Haybittle-Peto type rule based on the 99.9% confidence interval in each interim analysis for both superiority and non-inferiority comparisons [54]. See **Section 0** for details on DMC membership.

9.5 ANALYSIS PLAN (BRIEF)

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

The primary analysis population is intention-to-treat, including all randomised children, regardless of treatment received. This corresponds to estimating the impact of the effectiveness of the strategies of stepping down to oral amoxicillin vs co-amoxiclav and varying total duration of antibiotics. However, in secondary analyses we will also use inverse-probability weighting methods to adjust for deviation from randomised strategy, both duration of antibiotic treatment and oral-stepdown, which is a more efficient approach than defining a per-protocol population [55].

As follow-up is short (28 days post-randomisation) lost-to-follow-up should be low, and in each population, the primary comparison between randomised groups will be conducted using binomial regression, reported on the risk difference scale (following the sample size calculation which is based on risk differences). The primary analysis will adjust for the randomisation stratification factors (site and the other factorial randomisation). The primary analysis will be conducted on observed data. Secondary analyses will use multiple imputation with chained estimating equations to impute outcomes for the small (5%) number of expected missing outcomes due to losses to follow-up before 28 days post-randomisation (the sample size calculation in **Section 9.3** includes an inflation factor to allow for this). Imputation will be done separately within each randomised group to allow for unknown interactions, and will be based on outcomes and main baseline characteristics as recommended. Duration-response curves will be estimated separately for oral amoxicillin and oral co-amoxiclav randomised groups using fractional polynomials to flexibly model the impact of duration on response following Quartagno et al [33]. A combined model will test whether there is evidence that these duration-response curves vary between co-amoxiclav and amoxicillin using main effects and interactions (i.e. subgroup effects), specifically the following key factors:

- site

- severity
- age
- HIV infection and exposure
- malnutrition (assessed by weight-for-height Z-scores, according to the WHO Growth Standards, and pedal oedema/MUAC)
- initial IV regimen (benzylpenicillin plus gentamicin or ampicillin plus gentamicin, vs benzylpenicillin or ampicillin alone, vs ceftriaxone alone or cefotaxime alone)
- prior oral/intramuscular antibiotics before hospitalisation for the index CAP episode
- baseline CRP (semi-quantitative, 10-40 vs 40-80 vs >80 mg/l)
- chest X-ray features (abnormal vs normal vs uninterpretable vs not done based on any chest X-ray up to and including 72h from admission).

Secondary outcome analyses will similarly use exact tests and binomial regression for binary outcomes, and t-tests and normal linear regression (potentially on transformed data depending on the observed data distribution, adjusted for baseline values) for continuous outcomes. Ranksum tests will be used if there is gross departure from normality that cannot be adequately addressed by data transformation. Adverse events will be summarised by body system.

A Statistical Analysis Plan will be written and approved by the Trial Management Group (TMG), Trial Steering Committee (TSC) and the DMC before the first interim analysis is reviewed by the DMC.

10 ANCILLARY STUDIES

10.1 PHARMACOKINETIC SUBSTUDIES

The aim of the PK substudies with PediCAP-A and PediCAP-B is to characterise the PK of oral amoxicillin and clavulanate (clavulanic acid) in the PediCAP population. Since clavulanic acid is not expected to affect amoxicillin PK, the model developed will be used to infer expected amoxicillin exposure in all children receiving oral step-down the main trial. Very little oral absorption data on clavulanic acid has been published in children, and hence the investigation of 7:1, 4:1 and 14:1 ratios will enable estimation of clavulanic acid oral absorption and dose linearity.

The overall objectives of the nested PK substudies are therefore to develop a PK model of amoxicillin and clavulanic acid from which the PK of the whole PediCAP population can be inferred, and to investigate clavulanic acid linearity across 4:1, 7:1 and 14:1 ratio formulations.

These objectives will be achieved by PK sampling in two groups of children.

10.1.1 PHARMACOKINETIC SAMPLING IN CHILDREN RANDOMISED IN THE MAIN TRIAL (PEDICAP-A)

A subset of children joining the main trial (PediCAP-A) will be approached for additional written informed consent to take part in a PK substudy of the 7:1 co-amoxiclav formulation if they are randomised to oral co-amoxiclav step-down. In total, 60 children with a complete set of PK samples (defined below) will be included (out of the total 500 randomised to 7:1 co-amoxiclav in PediCAP-A), targeting a minimum of 6 children per weight-band from 6kg up to 25kg to ensure a minimum dataset is generated for each proposed dose in the main weight range.

PK sampling will occur immediately before and then after the first morning dose and will consist of 5 samples per child weighing 6kg or more (2ml per sample); e.g. before observed dosing (5-10 min pre-dose), during early absorption (0.25-1h post dose), around the expected Cmax (1-2h), during early disposition (2-6h), and in the terminal phase (6-12h). Optimal design and model-based stochastic simulation-estimation will be used to determine the exact sampling windows (which will maximise the information obtained from sampling compared to fixed sampling times) and the allocation of children between the weight-bands, while keeping the total pre-specified sample size. Allowable blood draws are 10ml or more in 24h in unwell children weighing 5kg or more (**Appendix II**): any child weighing less than 5kg will have one (4kg) or two (3kg) of the 5 PK samples dropped (chosen according to the optimal design) and will be considered to have a complete PK sample set (leading to total blood draws over 12h of 8ml and 6ml respectively). A cannula will be used to avoid repeated venepuncture, and anaesthetic cream to numb the child's skin.

Any child consenting to the PK substudy who does not have the complete set of PK samples taken for any reason (e.g. refusal of later samples) will be replaced, to give a total of 60 children with a complete set of PK samples. PK data from samples from any children not providing the full set will nonetheless be pooled for the model-based analysis (see below). For some children, this may require a short period of additional hospitalisation (e.g. if they would otherwise have been discharged mid-morning, but need to stay until the evening for the final PK sample), which will be clearly explained to each parent/carer, has been costed as part of the trial, and will not contribute to the trial secondary endpoint, length-of-stay. Parents/carers will be given travel money for the extra PK day.

10.1.2 PARALLEL PHASE II PHARMACOKINETIC TRIAL (PEDICAP-B)

An additional, but separate, 120 children meeting the same eligibility criteria as for the main trial (**Section 3**) will undergo randomisation to two different co-amoxiclav formulation strengths, 4:1 vs

14:1 in a parallel Phase II PK trial (PediCAP-B), and all 120 will undergo intensive PK sampling exactly as described in **Section 10.1.1** above.

Randomisation (stratified by weight band) will continue until 60 children with complete PK samples (as defined above) have been enrolled for each formulation strength. As for the 7:1 formulation, PK data from samples from any children not providing the full set will nonetheless be pooled for the model-based analysis.

10.1.3 ASSAYS AND ANALYSIS

Samples will be shipped to a central laboratory in the UK for processing. The PK MOP contains full details of PK procedures and sample handling, including storing plasma aliquots separately for shipping. Plasma concentrations will be determined with highly-sensitive LC-MS/MS methods.

A population PK model will be developed to identify and quantify the effect of covariates including body size (e.g. weight), age, renal function, HIV infection/exposure status, and malnutrition. Secondary PK outcomes (area under the time-concentration curve, maximum and minimum concentration, time to maximum concentration) will be derived from the model and compared across weight-bands using geometric means and geometric mean ratios. Models will then be extended to include information on the different strengths, and in particular associations with side-effects (e.g. intensity and severity of diarrhoea) will be estimated for the different formulation strengths. All data manipulations and model post-processing will be done in R (version 3.4 or higher) [56] and the PK model will be produced in NONMEM version 7.4 or higher.

No formal power calculation has been performed. Based on previous studies, 60 evaluable children in each formulation group should be sufficient to assess the association between normalised dose and area under the curve of clavulanic acid. Since population pharmacokinetic analysis will be performed, it has also been shown that approximately 50 children in total are required to detect most clinically meaningful covariate effects (in this case whether clavulanic acid PK are linear). Hence, with 60 children per group, this substudy should be adequately powered to identify important predictors of both amoxicillin and clavulanate exposure, particularly the impact of malnutrition/under-nourishment.

The population PK model will enable us to predict the PK of all 1220 children and conduct population dose-response modelling (PK-pharmacodynamic (PK-PD) model) In particular, we will investigate associations between trial primary and secondary outcomes and simulated time above the minimum inhibitory concentration (MIC), the key target for beta-lactam antibiotics. We will also use the PK model together with dosing and covariates information, to simulate expected PK profiles and calculate the probability of target attainment in this population under any given dose.

10.2 MICROBIOLOGICAL SUBSTUDY

The primary objective of the microbiological substudy is to evaluate the impact of amoxicillin and co-amoxiclav oral treatment and the duration of hospitalisation and of antibiotic treatment on prevalence and resistance of pathogens causing CAP, and on the carriage of multidrug-resistant Gram-negative bacteria (MDR-GNB) in children, in comparison with continuous IV treatment. A secondary objective is to assess the dynamics of the causative pathogens and their underlying resistance mechanisms under and following therapy. The goal is to answer in depth questions regarding the potential impact of antibiotic management strategies on antimicrobial resistance by using novel microbiological methods to determine how these strategies relate to resistance in colonizing bacteria. Recognizing the serious threat of antibacterial resistance to future African child health, this will enable outcomes beyond the immediate health benefits of narrower compared to

broader-spectrum antibiotics to be taken into account in clinical decision-making about antibiotic treatment strategies in children initially managed in hospital for severe pneumonia in sub-Saharan Africa.

66 children randomised in each site (total 330) will be approached for consent for microbiological characterisation of the commensal nasopharyngeal and faecal flora through nasopharyngeal and peri-rectal sampling (or faecal sampling from a child wearing a nappy, or who passes a stool). Children in the microbiological substudy will also be asked to provide peri-rectal swabs at discharge and at the week 4 face-to-face follow-up (or samples from nappy/passed stool as above). Each child will also provide one additional nasopharyngeal swab after trial entry, at either discharge or week 4 (determined by an additional randomisation to ensure comparability). Only two nasopharyngeal samples are collected because these are more invasive for the child than peri-rectal/faecal sampling. Randomisation between discharge and week 4 for the second nasopharyngeal swab will ensure that changes in nasal flora can be assessed unbiasedly at both timepoints, without requiring three swabs per child.

A MOP will guide participating laboratories in the processes of sample collection and management locally, and in order to optimise and standardise local procedures. The manual will include detailed instructions on sampling, transport and storage of study samples and strains, and will be made available online and through written materials. Training will be provided for PIs and other key local personnel from participating clinical sites to ensure optimal and standardised sampling from all participating children including quality assurance exercises and quality control. The samples will be stored at -80°C for batched transfer to the University of Antwerp for analysis. Strain types and resistance genes of isolated bacteria will be further investigated.

Briefly, peri-rectal and nasopharyngeal swabs will be transferred frozen at -80°C, and then be thawed and processed at the University of Antwerp. Total bacterial DNA will be extracted from uncultured swab samples following standard procedures, and shotgun sequenced using Illumina technology. We will determine species and functional richness and diversity and determine phylogenetic and functional composition of the metagenome. As a complementary methodology to the functional screen mentioned above, we will also mine the nasopharyngeal and gut microbiome for known antibiotic resistance genes, as well as further investigate those that have detected in the functional screen. Based upon a manually compiled list of target resistance genes, hidden Markov models will be built and used to screen the nasopharyngeal and gastrointestinal metagenomes generated within this project. This will allow the quantification of different resistance pools in the paediatric population, and the impact of antibiotic management strategies and hospitalisation on amplification of these pools.

10.3 HEALTH-ECONOMIC ANALYSES

We will assess the full economic costs of each randomised group from time of admission to hospital until death or 28 days' follow-up. While the trial defines re-admission to hospital as an endpoint, for an economic evaluation, hospital re-admission will be included as a cost. A full economic costing approach includes financial as well as opportunity costs and is necessitated by the reality of severely constrained capacity within LMIC health systems. Our approach to costing establishes the utilisation of health services (e.g. inpatient days, diagnostic tests, medication and oxygen) directly from trial data specific to each randomised group. Within a decision analytic modelling framework, these utilisation estimates are multiplied by the full economic or site-specific unit cost of each service, diagnostic test or medicine. Unit costs are computed using a combined bottom up and step down approach, as appropriate [57]. When valuing resources within the cost analysis that are paid from

the research budget, we will use routine public sector salaries for staff and will seek to cost antibiotics that are sourced specifically for the trial at a level commensurate with a potential public sector funding decision in LMIC. In addition, care will be taken to exclude any costs that are incurred only as part of the research.

The data collection at the health system level will be complemented by a comprehensive assessment of costs incurred by households. These costs do not only include out-of-pocket expenditures for medical services (which we expect to be small because the trial will cover related costs), but also costs for transport to facilities, local food and accommodation, and income losses due to absences from work.

Once we have estimated our unit costs and utilisation, we will build a decision analytic model in order to estimate the cost per child treated within each randomised group, from time of first admission until 28 days follow-up. Deterministic sensitivity analyses will assess the impact of key parameter uncertainty (e.g. the cost of antibiotics within a scale-up scenario) and probabilistic sensitivity analysis will assess uncertainty around the relevant utilisation and outcome estimates from the trial [57]. Then, using outcome data from the trial and secondary sources as necessary, we will estimate a range of incremental cost-effectiveness ratios, including the cost per additional child cured, cost per life-year gained, and cost per DALY averted. DALYs are the addition of Years of Life Lost (YLL) and Years Lived with Disability (YLD) [57, 58]. DALYs will be calculated in two steps. First, for children dying during the trial, the life-year estimate (as described above) is equivalent to YLL. Secondly, for all children, a disability weight will be applied to an estimate of the days spent with CAP. This disability weight for childhood CAP will be sourced from the WHO [59]. Put together, this will enable an estimation of DALYs, and DALYs averted within each trial group.

One of the key intentions of economic evaluation is to promote health care decisions that maximize population health within the available budget. To achieve this, a generic measure of outcome is needed in order to compare (in theory) across the full spectrum of diseases and patient groups within the particular setting [60]. Following this logic, the key ratio to be used will be the incremental cost per DALY averted (the incremental cost-effectiveness ratio (ICER)). Determining cost-effectiveness then requires the comparison of this ICER to other claims on limited resources (represented by a cost-effectiveness threshold (CET)). If the ICER<CET the intervention may be deemed “cost-effective”. The choice of CET will be based upon knowledge of the ICERs in recent funding decisions within the country health systems as well as international estimates.

One of our main economic hypotheses is that the earlier discharge of children will substantially lower the financial and time burden to families, and that these differences will be particularly important for the poorest strata in each country. To quantify these differences, we will collect data on household’s human capital and living conditions and then classify households into site-specific quintiles. We will then estimate interacted impact models in a first step to assess whether health impacts vary across socio-economic subgroups. In a second step, we will quantify the total financial burden for all households, and quantify the share of households experiencing catastrophic expenditures. Catastrophic expenditure will be defined as total cost exceeding specific fractions of total monthly household income, with thresholds ranging between 10 and 50% [61]. Household incomes will be computed based on the observed asset holdings using national surveys as references points [62]. The generated evidence will complement the standard cost-effectiveness analysis (which abstracts from equity aspects) by assessing the overall equity and impact of these treatment regimens in general, and by assessing the extent to which these regimens can reduce socioeconomic gaps in particular.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the Declaration of Helsinki version 7 of 2013 [63].

It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the EU General Data Protection Regulation 2016/679 and the UK Data Protection Act (DPA number: Z6364106).

11.1.2 SITE COMPLIANCE

The sites will comply with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP) and applicable national regulations. An agreement will be in place between the sites and the CTU, setting out respective roles and responsibilities (see **Section 13**).

The sites will inform the CTU as soon as they are aware of a possible serious breach of compliance, so that the CTU can report this breach as necessary. For the purposes of this protocol, a 'serious breach' is one that is likely to affect to a significant degree:

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

11.1.3 DATA COLLECTION & RETENTION

CRFs\worksheets, 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 a minimum of 25 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent or equivalent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. The data may be subject to an audit by the competent authorities. Medical files of children in the trial should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

11.2 ETHICAL CONDUCT

11.2.1 ETHICAL CONSIDERATIONS

The risks of the safety of children enrolled in the trial relate to the inherent risks of the drugs being studied. All drugs have side-effects, including antibiotics. The main possible side-effects of both the drugs being tested in the trial (amoxicillin and co-amoxiclav) are diarrhoea, and nausea/vomiting. Very rarely children can have an allergic reaction to amoxicillin. However, those randomised to oral step-down will have a shorter period with IV lines, which may reduce complications. Parents/carers of children randomised to 5 days' IV will receive travel costs for any additional days their child remains in hospital solely for the purpose of receiving intravenous antibiotics within the trial, since a few of these children might otherwise be discharged early on oral antibiotics depending on local practice (site-specific). The trial will directly evaluate whether these potential risks are outweighed by potential benefits.

An additional CRP test is required for eligibility: this is to avoid including a large number of children in the trial without bacterial infections (who therefore do not need antibiotics) and hence potentially miss important effects in children with bacterial infections. Some of the trial sites already do a

baseline CRP in children admitted with CAP. For the trial we will standardise CRP testing to use a point-of-care device which can be done using a finger or heel prick rather than an additional venous blood draw. Admitted children will have finger/heel pricks for glucose measurement during admission and these are more acceptable to parents/carers.

Some children will also have blood taken for clinical management and also for research blood tests (PK in particular). The volumes of blood required will be minimized wherever possible and are within the maximum locally agreed volumes. For intensive PK, a venous cannula will be used so that children do not undergo repeated venepuncture. We will also use anaesthetic cream to reduce the impact of cannulisation in children having blood draws for the pharmacokinetic substudy. Travel costs will be provided to parents/carers for the PK day (when their child may need to spend additional time in hospital). Nasopharyngeal and peri-rectal swabs will be collected if consent is given in a subset of children. Samples will be taken from a nappy if the child is wearing one or directly of faecal material if a stool is passed, avoiding additional samples being taken. The risks of rectal swabbing are small and will be minimised by training and adherence to a standardised MOP.

For staff involved in the trial, the only risk occurs from venepuncture.

Children will be informed fully of known risks and possible benefits by means of a patient information sheet for parents/carers, and this will be reinforced by discussions with the trial research teams at the individual sites prior to enrolment.

Children's confidentiality will be maintained throughout the trial. Data submitted on CRFs\worksheets to trial sites and CTU, and samples sent to central testing facilities, will be identified only by the Study ID (including random check letters to improve accuracy of identification, as well as date, and time for PK samples).

Week 4 follow-up will be face-to-face wherever possible for all children, and other follow-up contacts will be via telephone where possible. Travel costs for the additional 4-week visit will be provided to compensate participating families for their time, in line with local ethics policies.

Cost and utilisation data will be collected at the site level and through CRFs\worksheets. This data will remain anonymous (in terms of staff and patient names and identifiers) and will only be used for the purpose of estimating the cost and cost-effectiveness of different treatment strategies as well as their equity impacts at household level.

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 they feel it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the child 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/carer 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 further care.

11.3 COMPETENT AUTHORITY APPROVALS

This protocol will be submitted to the national competent or equivalent authority, as appropriate in each country where the trial will be run.

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 will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

11.4 TRIAL CLOSURE

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

12 INDEMNITY

The Sponsor of the trial is Fondazione PENTA ONLUS. In consideration of the agreement by the Principal Investigator at each site to supervise the trial, Fondazione PENTA ONLUS undertakes to indemnify the Principal Investigator at each site and the institutions which participate in the trial and their employees and agents in respect of any claims made against them by any third party which arises out of or as a result of the supervision or conduct of the trial (including any claim arising in respect of the technical procedures described in the protocol which children would not have been exposed to but for their participation in the trial). Full details of the Indemnity agreement are given in a separate document. Cover against claims arising from medical negligence is not included.

13 FINANCE

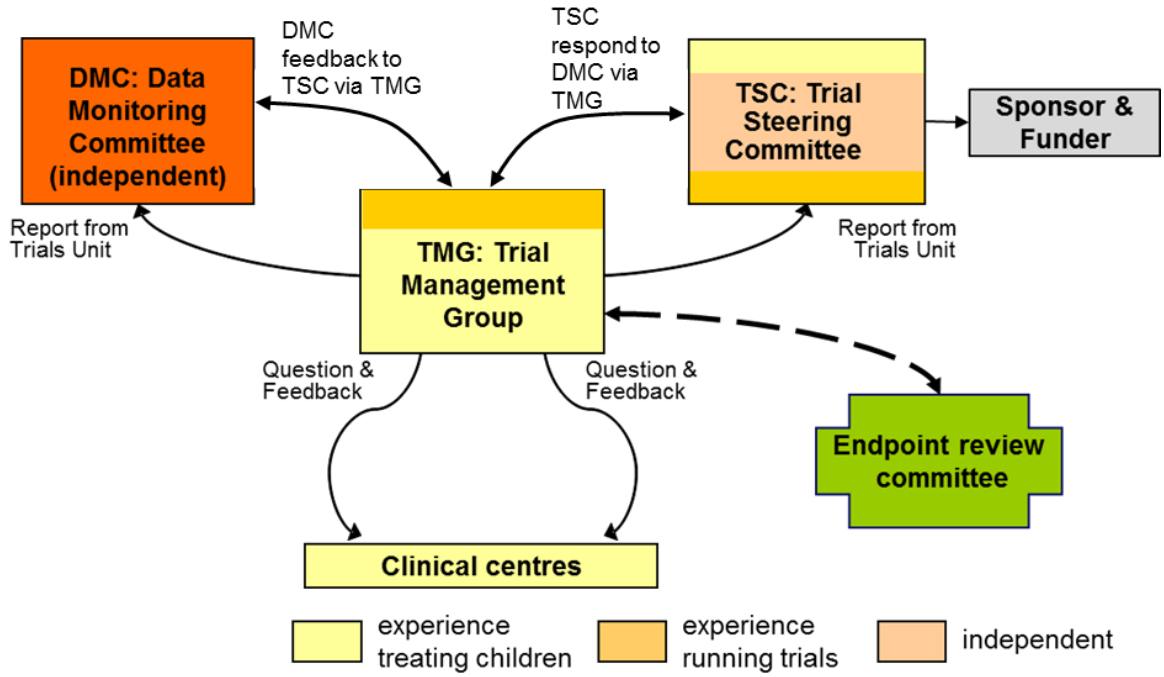
PediCAP is funded by the European Developing Countries Clinical Trials Partnership [RIA2017MC-2023]. In kind support is provided by the UK MRC to the MRC CTU at UCL.

A written agreement with the site PI and Fondazione PENTA ONLUS will outline the funding arrangements to sites.

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 7**.

Figure 7: Trial Organogram



Note: DMC are sometimes referred to as Data Safety Monitoring Boards (DSMB). Trial Steering Committee includes community representatives, see below.

14.1 SITE TRIAL MANAGEMENT TEAMS (TMT)

A Trial Management Team (TMT) will be formed at each site to conduct the day-to-day management of the trial at the site. This will include the investigators and trial staff at the site. These groups will meet every one to two weeks and will be chaired by the Principal Investigator or Co-Principal Investigator at the site. The group will discuss issues related to the progress of the trial at the site and to ensure that the trial is running well.

There will be a similar trial management team formed to conduct the day-to-day management of the trial at the MRC. This will include the Chief Investigator, trial statisticians, trial physician, clinical project manager, trial manager (TM) and data manager. The group will meet at least once per month, although may meet more often if required.

14.2 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, site Principal Investigators, co-investigators and Trial Managers, other lead investigators (clinical and non-clinical) and members of the CTU. It will meet approximately once a year in-person and will hold a regular

teleconference at approximately monthly intervals at which sites will summarise progress and challenges and bring up for discussion any difficulties, as well as discuss and decide matters of general importance for the trial. This group will be chaired by the Chief Investigator and all decisions regarding the overall running of the trial will be made in this forum with the exception of matters of fundamental importance to the viability of the trial or that require major changes to the protocol. These will be referred to the Trial Steering Committee (TSC). The full details can be found in the TMG Charter.

14.3 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair and Community Advisory Group (CAG) contributors. 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 will be detailed in the TSC Charter.

Professor Elizabeth Molyneux will Chair the PediCAP Trial Steering Committee; she has substantial experience as a paediatrician working in low-income countries and also chairing Steering Committees for large pragmatic paediatric trials including FEAST, TRACT [46] (also a factorial trial) and COAST [47]. The TSC will also include as independent voting members

- Dr Shamim Qazi (a leading expert in the field, until recently at the Department of Maternal Newborn Child and Adolescent Health, World Health Organization, Geneva),
- Dr Somwe wa Somwe (Paediatrician at the University Teaching Hospital, Lusaka, Zambia),
- Prof Elizabeth Obimbo (Professor, Head of the Department of Paediatrics and Child Health at the University of Nairobi, Kenya)
- Prof Robin Green (Professor at the Department of Paediatrics and Child Health, University of Pretoria, South Africa).
- A community representative (TBA) will also be an independent member of the TSC.

The trial team will be represented by the principal investigator from each country (UK Sharland, South Africa Madhi, Uganda Musiime, Zambia Mulenga, Zimbabwe Mujuru) (non-independent voting members). Non-voting observers will include the Trial Statistician, representatives of the Sponsor (Fondazione PENTA ONLUS) and funder (EDCTP) and the pharmaceutical company donating drugs (Sandoz).

Each site would either use their existing Community Advisory Group (CAG) or form a specific patient liaison group who would be responsible for liaising with the community representative on the TSC, would feedback concerns and questions from the community and also hear about the latest developments in the trial and the wider scientific community.

14.4 DATA MONITORING COMMITTEE (DMC)

An independent Data Monitoring Committee (DMC) will be formed. The DMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the DMC will be produced by the CTU statisticians. The DMC will meet within 6 months of the trial opening; the frequency of meetings will be determined by the DMC. The DMC will consider data using the statistical analysis plan (see **Section 9.5**) and will advise the TSC. The DMC can recommend premature closure or reporting of the trial, or that recruitment to any randomised group be discontinued.

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

The Chair of the PediCAP DMC will be Prof Tim Peto, Nuffield Dept of Medicine, Oxford, UK. Additional independent members will be

- Professor Haroon Saloojee, University of the Witswatersrand, South Africa (President of the South African Paediatric Association)
- Dr Margaret Siwale, Lusaka Trust Hospital, Lusaka, Zambia
- Dr Andrew Prendergast, Zvitambo Institute for Maternal & Child Health Research, Harare Zimbabwe and Queen Mary University of London, London, UK
- Dr Mainga Hamaluba, Head of Clinical Trials at KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya.

14.5 ENDPOINT REVIEW COMMITTEE

An Endpoint Review Committee will be appointed, whose remit (as defined in separate Terms of Reference) will be to determine the validity of potential clinical endpoints in terms of meeting the standard criteria, and particularly whether they are CAP-related. It will have an independent Chair (not involved with the day-to-day running of the trial at sites) and will include Project Leaders from each site as well as other independent clinicians. No member will review endpoints from their own site. Review will be conducted blinded to randomised group.

14.6 ROLE OF STUDY SPONSOR

Fondazione PENTA ONLUS is the Sponsor of PediCAP and delegates this responsibility to the MRC CTU at UCL to oversee the implementation of the study by ensuring that arrangements are put into place for adequate management, monitoring, analysis and reporting of the trial.

15 PATIENT AND PUBLIC INVOLVEMENT

As paediatric CAP is an acute, rather than a chronic, illness, it does not have existing support groups that can be approached about the trial and its design. We have consulted widely with various bodies about the acceptability and issues around the design, but are focussing on work with local groups during the set-up phase of the trial.

A Community Advisory Group (CAG) will be established based on public groups and community advisory boards that have been developed in participating countries in other disease areas, and will also try and recruit children and families who have direct experience of being admitted with pneumonia to gain relevant views on the trial. The CAG will be involved in the trial sensitisation and dissemination and will deliberate on issues including:

- Safeguard of patient information
- How best to inform caregivers about the trial
- Views of the community about acute infection research, and barriers to participation
- How to communicate the results of the research to children, caregivers and the community (both local to the sites, and the international community)

The CAG will include representatives from the local community of each site (potential representatives will be identified in collaboration with each site PI during a stakeholder mapping process), and may be elected from similar community-based liaison groups involved in other studies conducted at each site, if available.

The CAG will meet approximately annually, either at face-to-face meetings around TSC meetings, or via teleconference. They will also have representation on the TSC.

16 PUBLICATION AND DISSEMINATION OF RESULTS

The PediCAP TSC is the custodian of the data and specimens generated from the PediCAP trial; PediCAP trial data are not the property of individual participating investigators or health care facilities where the data were generated.

It is anticipated that a number of opportunities will arise for publication during the course of and following completion of the PediCAP trial. Publications include papers (including abstracts) for presentation at national and international meetings, as well as the preparation of manuscripts for peer-reviewed publication. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the *Lancet* and from the publication policies used in other clinical trials coordinated by the MRC CTU at UCL:

- All publications are to be approved by the TMG and TSC before submission for publication. Any publication arising before the end of the trial (not by randomised groups) will also be approved by the DMC in order to ensure that the primary objective of the trial (the randomised comparison) is not compromised. In particular, no analyses by randomised group of any outcome (primary, secondary or other) in either the main trial (PediCAP-A) or the Phase II PK trial (PediCAP-B) or any of the associated substudies will be conducted or presented before the end of the trial, other than those for interim review by the DMC. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

- In line with MRC policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial should be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. All conference presentations will be made available as soon as possible after the event via the PediCAP website. All publications will acknowledge the trial's funding sources by including the statement provided by the funder, and displaying the logos on posters and presentations.

- For all publications, the TMG will nominate a chairperson or approve an individual's request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.

- The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee, together with all relevant expert advisors and members of the ERC, TSC and DMC. All families who participated in the trial will be thanked as a group (not by name). In principle, substudy reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub-studies must have a made a substantive academic or project management contribution to the work that is being presented. "Substantive" must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of children who contributed data to any set of analyses contained in the manuscript and/or the conduct of

analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

- The data derived from this clinical trial are considered the property of the PediCAP TSC. The presentation or publication of any data collected by the participating investigators on children entered into this trial is under the direct control of the TMG and TSC (and the DMC before the end of the trial). This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC (and the DMC before the end of the trial), they will be encouraged to develop sub-studies or propose analyses subject to the approval by the TMG and TSC (and the DMC before the end of the trial). Any requests for access to raw data will be welcomed as long as they are scientifically valid and do not conflict with the integrity of the trial or ongoing analyses by the trial team.

Outcome data by randomised group will not be revealed to the participating investigators until the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The DMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons, or if a definitive answer is reached earlier than the scheduled end of the trial.

17 DATA AND/OR SAMPLE SHARING

Data will be shared according to the CTU's controlled access approach [64], based on the following principles:

- No data should be released that would compromise an ongoing trial or study.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Data will be available for sharing after publication of the primary trial results. Researchers wishing to access data should contact the Trial Management Group in the first instance.

18 PROTOCOL AMENDMENTS

Changes from Protocol v1.0 to v2.0	
Section	**Change/addition/deletion**
Front page	• Update to date and version
Trial Administration	• Updates to MRC CTU data manager contacts and qualifications
1.5	• 'Goals of PediCAP' updated to corrected age of children 2 months to 3 months
2	• Additional sentence to note recruitment target is 220 children at each site however targets may be modified as required.
5.7	• Additional text to clarify the parent/carer/child is not required to give a reason for discontinuing treatment.
6.1.1	• Additional sentence to state children will be weighed at the week 4 face to face visit.
6.9	• Additional text to clarify the trial will distinguish between stopping of trial treatment and stopping of trial follow-up.
9.4	• Additional sentence explaining the Data Monitoring Committee Charter will also contain a description of stopping rules and/or guidelines.
Changes from Protocol v2.0 to v3.0	
Section	**Change/addition/deletion**
Front page General Information Summary of Trial	• ISRCTN number added
Front page	• Signatory for Fondazione PENTA ONLUS updated
General Information 8.3.2 11.1.1	• Additional text to confirm that the principles of the EU General Data Protection Regulation 2016/679 will be followed.
General Information	• MRC CTU staff details updated. • Pharmacology - UCL lab replaced with Analytical Services International Ltd (ASI) lab based at St. George's University of London. • Pharmacology – ASI lab contact added.
Trial diagram Synopsis 3.3 3.5 5.1 10.1.1, 10.1.2	• Clarification that each child would be approached for EITHER PediCAP-A OR PediCAP-B (not both and not sequentially), and that 60 of 500 children randomised to co-amoxiclav 7:1 in PediCAP-A would undergo PK, whereas all 120 children randomised to co-amoxiclav 4:1 vs 14:1 would undergo PK.
Trial flow diagram (p12) Flowsheet p17 6.3 10.2	• Amend second nasopharyngeal swab to be taken at either discharge or week 4 visit in children in the microbiology substudy (randomised to ensure comparability), rather than at week 4 in all children in the microbiology substudy.

	• Clarification that microbiology substudy children will be "among the first enrolled" rather than "the first" because additional consent is sought for this.
1.5	• Renamed goals of PediCAP to objectives and clarified that answering the research questions is the objective of the trial, distinguishing between primary and secondary objectives.
2.1.4	• Details added on source data requirements.
3.1	• Criteria 4c -Addition of moderate/severe malnutrition as a danger sign following recent consensus committee recommendation (Goodman et al Lancet Resp Med 2019) • Criteria 7 – Clarification that parents/carers must be willing to accept the possible allocation of 5 days IV antibiotics if joining PediCAP-A
3.2	• Clarification that exclusion for allergy was intended to apply to the class of penicillins, not just the specific drug penicillin
3.3.2 6.3 10.1.1 10.2	• Removal of the PK substudy and microbiological substudy children being "the first" children to be enrolled, as the substudies will not open until later.
3.5	• Added the short information leaflet to be given to parents/carers when initially approached for the study
4.1	• Removal of the possibility to use randomisation cards. All sites will use the online database.
5.2.1	• Removed "(i.e. a minimum of two intravenous doses)" as this will depend on the dosing regimen of the antibiotics.
5.2.1	• Removed procaine benzylpenicillin from Table 6 as no PediCAP sites use this as Standard of Care treatment.
5.3.1.A	• Corrected dosing of Co-amoxiclav 14:1 in 20-<25kg weight band in Table 7.
6.5	• Clarification on haematology results collected, here and on the footnotes of the Trial Assessment Schedule.
7.1.1	• Confirmation that the IV antibiotics are included as IMP.
7.3.1.E	• Timeframe that sites should notify CTU of SAEs amended from "the time of randomisation" to "the time that main informed consent is signed".
8.3.1	• Added "and notable events"
9.2.3	• Clarification that symptoms will be self-reported by the parent/carer at each visit and that diaries will not be used.
9.5	• Clarification that analysis of primary outcome will be reported on risk difference scale.
11.1.3	• Updated the length of time that trial documentation should be held for after the trial from 15 years to 25 years. This is in line with the new EU Clinical Trial Regulations.
16	• Clarification that all publications should be submitted to Open Access journals. • Confirmation that all publications will acknowledge the trial's funding sources.
Throughout	• Replaced "CRF" with "CRF/worksheet" to reflect the fact that new electronic data capture systems enter data from paper worksheets, with the electronic data being considered the CRF.
Throughout	• "Trial Number" amended to "Study ID"
Throughout	• "Enrolment Form" amended to "Baseline Form"

Throughout	• Clarified that digital copies of x-rays will be collected *where possible*

19 REFERENCES

1. Walker, C.L.F., et al., *Childhood Pneumonia and Diarrhoea 1 Global burden of childhood pneumonia and diarrhoea.* Lancet, 2013. **381**(9875): p. 1405-1416.
2. Liu, L., et al., *Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis.* The Lancet, 2015. **385**(9966): p. 430-440.
3. Global Burden of Disease Lower Respiratory Infections Collaborators, *Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.* Lancet Infect Dis, 2018. **18**(11): p. 1191-1210.
4. Lazzerini, M., et al., *Mortality and its risk factors in Malawian children admitted to hospital with clinical pneumonia, 2001–12: a retrospective observational study.* The Lancet Global health, 2016. **4**(1): p. e57-e68.
5. Enarson, P.M., et al., *Reducing deaths from severe pneumonia in children in Malawi by improving delivery of pneumonia case management.* PLoS One, 2014. **9**(7): p. e102955.
6. Izadnegahdar, R., et al., *Childhood pneumonia in developing countries.* The Lancet Respiratory Medicine, 2013. **1**(7): p. 574-584.
7. Duke, T., et al., *Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial.* The Lancet, 2002. **359**(9305): p. 474-480.
8. Sutcliffe, C.G., et al., *A clinical guidance tool to improve the care of children hospitalized with severe pneumonia in Lusaka, Zambia.* BMC pediatrics, 2016. **16**(1): p. 136.
9. English, L., et al., *Pediatric out-of-hospital deaths following hospital discharge: a mixed-methods study.* African health sciences, 2016. **16**(4): p. 883-891.
10. World Health Organization and UNICEF, *Global action plan for prevention and control of pneumonia (GAPP)*. 2009, Geneva: World Health Organization.
11. Omidvari, K., et al., *Early transition to oral antibiotic therapy for community-acquired pneumonia: duration of therapy, clinical outcomes, and cost analysis.* Respiratory medicine, 1998. **92**(8): p. 1032-1039.
12. Howie, S.R., et al., *Etiology of severe childhood pneumonia in the Gambia, West Africa, determined by conventional and molecular microbiological analyses of lung and pleural aspirate samples.* Clinical infectious diseases, 2014. **59**(5): p. 682-685.
13. Madhi, S.A. and M.C. Nunes, *The potential impact of pneumococcal conjugate vaccine in Africa: considerations and early lessons learned from the South African experience.* Human vaccines & immunotherapeutics, 2016. **12**(2): p. 314-325.
14. Reiss-Mandel, A. and G. Regev-Yochay, *Staphylococcus aureus and Streptococcus pneumoniae interaction and response to pneumococcal vaccination: Myth or reality?* Human vaccines & immunotherapeutics, 2016. **12**(2): p. 351-357.
15. Peace, N., O. Olubukola, and A. Moshood, *Stability of reconstituted amoxicillin clavulanate potassium under simulated in-home storage conditions.* Journal of Applied Pharmaceutical Science, 2012. **2**(1): p. 28.
16. Lassi, Z.S., A. Imdad, and Z.A. Bhutta, *Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months.* The Cochrane Library, 2015.
17. Haider, B.A., M.A. Saeed, and Z.A. Bhutta, *Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months.* Cochrane Database Syst Rev, 2008. **2**.
18. Uranga, A., et al., *Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial.* JAMA internal medicine, 2016. **176**(9): p. 1257-1265.

19. el Moussaoui, R., et al., *Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study*. 2006, British Medical Journal Publishing Group.
20. Soofi, S., et al., *Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial.* The Lancet, 2012. **379**(9817): p. 729-737.
21. Hazir, T., et al., *Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial.* The Lancet, 2008. **371**(9606): p. 49-56.
22. Addo-Yobo, E., et al., *Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study.* The Lancet, 2004. **364**(9440): p. 1141-1148.
23. Esposito, S., et al., *Antibiotic therapy for pediatric community-acquired pneumonia: do we know when, what and for how long to treat?* The Pediatric infectious disease journal, 2012. **31**(6): p. e78-85.
24. Appelbaum, P.C., *Microbiological and pharmacodynamic considerations in the treatment of infection due to antimicrobial-resistant Streptococcus pneumoniae.* Clinical infectious diseases, 2000. **31**(Supplement_2): p. S29-S34.
25. Bradley, J.S., et al., *The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America.* Clinical infectious diseases, 2011. **53**(7): p. e25-e76.
26. Williams, P.C., D. Isaacs, and J.A. Berkley, *Antimicrobial resistance among children in sub-Saharan Africa.* The Lancet Infectious Diseases, 2018. **18**(2): p. e33-e44.
27. World Health Organization, *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses*. 2013: World Health Organization.
28. World Health Organization, *Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries.* 2014.
29. Zhang, S., et al., *Cost of management of severe pneumonia in young children: systematic analysis.* Journal of global health, 2016. **6**(1).
30. World Health Organization, *Revised WHO classification and treatment of pneumonia in children at health facilities: implications for policy and implementation*. 2014, World Health Organization.
31. Kuehn, J., et al., *Reported rates of diarrhea following oral penicillin therapy in pediatric clinical trials.* The Journal of Pediatric Pharmacology and Therapeutics, 2015. **20**(2): p. 90-104.
32. Costelloe, C., et al., *Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis.* Bmj, 2010. **340**: p. c2096.
33. Quartagno, M., et al., *Rethinking non-inferiority: a practical trial design for optimising treatment duration.* Clinical Trials, 2018: p. 1740774518778027.
34. Spellberg, B., *The new antibiotic mantra—"shorter is better".* JAMA internal medicine, 2016. **176**(9): p. 1254-1255.
35. Nelson, A.N., et al., *Optimal duration of antimicrobial therapy for uncomplicated Gram-negative bloodstream infections.* Infection, 2017. **45**(5): p. 613-620.
36. Sharland, M., et al., *Manual of childhood infections: the blue book*. 2016: Oxford University Press.
37. Paediatric Formulary Committee, *BNF for Children 2016-2017*. Vol. 12. 2016, London: BMJ Group, Pharmaceutical Press, and RCPCH Publications.
38. *National Treatment Guidelines for Antimicrobial Use in Infectious Diseases*, G.o.I. Ministry of Health & Family Welfare, Editor. 2016.

39. AAP Committee on Infectious Diseases, *Red Book (2018): Report of the Committee on Infectious Diseases*. 31st ed, ed. D.W. Kimberlin, M.T. Brady, and M.A. Jackson. 2018.
40. *Standard Treatment Guidelines and Essential Drugs List for South Africa. Hospital Level, Paediatrics.*, P. National Department of Health, South Africa, Editor. 2013.
41. Nahirya-Ntege, P., et al., *Young HIV-infected children and their adult caregivers prefer tablets to syrup antiretroviral medications in Africa.* PLoS One, 2012. **7**(5): p. e36186.
42. Denti, P., et al. *An easy-to-use Paediatric Dosing Tool - Because one mg/kg dose does NOT fit all*. 2017; Available from: http://www.croiconference.org/sites/default/files/posters-2017/809_Denti.pdf.
43. Barker, C., et al. *Paediatric and neonatal co-amoxiclav population pharmacokinetics reveal poor target attainment: growing evidence of need for revisiting dosing regimens*. 2018; Available from: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=63449
44. Mrvos, R., T.L. Pummer, and E.P. Krenzelok, *Amoxicillin renal toxicity: how often does it occur?* Pediatric emergency care, 2013. **29**(5): p. 641-643.
45. Goodman, D., et al., *Challenges in the diagnosis of paediatric pneumonia in intervention field trials: recommendations from a pneumonia field trial working group.* Lancet Respir Med, 2019. **7**(12): p. 1068-1083.
46. Mpoya, A., et al., *Transfusion and Treatment of severe anaemia in African children (TRACT): a study protocol for a randomised controlled trial.* Trials, 2015. **16**(1): p. 593.
47. Maitland, K., et al., *Children's Oxygen Administration Strategies Trial (COAST): A randomised controlled trial of high flow versus oxygen versus control in African children with severe pneumonia.* Wellcome Open Research, 2017. **2:100 Last updated: 16 JAN 2018**.
48. Gillies, M., et al., *Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication.* Cmaj, 2015. **187**(1): p. E21-E31.
49. Salvo, F., et al., *Amoxicillin and amoxicillin plus clavulanate: a safety review.* Expert opinion on drug safety, 2009. **8**(1): p. 111-118.
50. Hsia, Y., et al., *Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries.* The Lancet Infectious Diseases, 2019. **19**(1): p. 67-75.
51. Falagas, M.E., et al., *Compliance with once-daily versus twice or thrice-daily administration of antibiotic regimens: a meta-analysis of randomized controlled trials.* PLoS One, 2015. **10**(1): p. e0116207.
52. Spellberg, B., et al., *Position paper: recommended design features of future clinical trials of antibacterial agents for community-acquired pneumonia.* Clin Infect Dis, 2008. **47 Suppl 3**: p. S249-65.
53. Fleming, T.R. and J.H. Powers, *Issues in noninferiority trials: the evidence in community-acquired pneumonia.* Clinical infectious diseases, 2008. **47**(Supplement_3): p. S108-S120.
54. Lai, T.L., M.C. Shih, and G. Zhu, *Modified Haybittle–Peto group sequential designs for testing superiority and non-inferiority hypotheses in clinical trials.* Statistics in medicine, 2006. **25**(7): p. 1149-1167.
55. Hernán, M.A. and J.M. Robins, *Per-protocol analyses of pragmatic trials.* N Engl J Med, 2017. **377**(14): p. 1391-1398.
56. R Core Team, *R: A language and environment for statistical computing.* 2013.
57. Drummond, M.F., et al., *Methods for the economic evaluation of health care programmes*. 2015: Oxford university press.
58. Murray, C.J., *Quantifying the burden of disease: the technical basis for disability-adjusted life years.* Bulletin of the World health Organization, 1994. **72**(3): p. 429.
59. World Health Organization, *The global burden of disease: 2004 update*. 2008.

60. Thokala, P., et al., *Cost-effectiveness thresholds: the past, the present and the future.* PharmacoEconomics, 2018. **36**(5): p. 509-522.
61. O'Donnell, O., et al., *Analyzing health equity using household survey data*. 2008, The World Bank.
62. Fink, G., et al., *Measuring socioeconomic inequalities with predicted absolute incomes rather than wealth quintiles: a comparative assessment using child stunting data from national surveys.* American journal of public health, 2017. **107**(4): p. 550-555.
63. World Medical Association, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* Journal of the American Medical Association, 2013. **310** (20): p. 2191–2194.
64. Smith, C.T., et al., *How should individual participant data (IPD) from publicly funded clinical trials be shared?* BMC medicine, 2015. **13**(1): p. 298.