Prophylactic Antibiotics To Prevent Chest Infections In Children With Neurological Impairment

Full explanatory title: Joint UK and Australia multicentre, randomised, double blind, placebo controlled pragmatic trial comparing 52 weeks of azithromycin to placebo in children with neurological impairment at risk of lower respiratory tract infection.

PARROT Protocol V3.0 12/03/2020

Trial Sponsor for the UK:
University of Liverpool,
2nd Floor Block D, Waterhouse Building,
3 Brownlow Street,
Liverpool,
L69 3GL

Trial Sponsor for Australia:
Menzies School of Health Research
John Mathews Building (Building 58)
Royal Darwin Hospital Campus
Rocklands Drive
Casuarina NT 0810

EudraCT number: 2019-001508-39

CTA Reference Number: 04196/0057/001

ISRCTN: To be confirmed

ANZCTR: ACTRN12619001597189

Research Ethics Ref: 20/NW/0047

UK Sponsor Ref: UoL001460

LIVERPOOL CLINICAL TRIALS CENTRE LCTC

UNIVERSITY OF LIVERPOOL

Alder Hey Children's NHS Foundation Trust

NIHR | National Institute for Health Research

In the UK, the PARROT trial is funded by the NIHR HTA programme (ref 16/17/01). In Australia, the PARROT trial is funded by the National Health and Medical Research Council (NHMRC, ref 1157228, APP1149332). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, NHMRC or the Department of Health and social care.

PROTOCOL APPROVAL

United Kingdom

I, the undersigned, hereby approve this clinical trial protocol:

Authorised by UK Chief Investigator:

Signature: _____ **Date:** _____

Professor Paul Stephen McNamara
Consultant in Paediatric Respiratory Medicine, Alder Hey Children's NHS Foundation Trust
Professor of Child Health, University of Liverpool
Institute in The Park
Alder Hey Children's Hospital
Eaton Road
Liverpool
L12 2AP

Authorised on behalf of UK Sponsor:

Signature: _____ **Date:** _____

Mr Alex Astor
Research Support Office
University of Liverpool
2nd Floor, Block D Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Authorised on behalf of the Lead Statistician:

Signature: _____ **Date:** _____

Dr Ashley Jones
Liverpool Clinical Trials Centre
University of Liverpool
Eaton Road
Liverpool
L12 2AP

PROTOCOL APPROVAL

Australia

I, the undersigned, hereby approve this clinical trial protocol:

Authorised by Australian Chief Investigator and on behalf of Australian Sponsor:

Signature: _____ **Date:** _____

Professor Anne Chang
Menzies School of Health Research
Charles Darwin University
Rocklands Drive
TIWI NT 0810

General Information

This document describes the PARROT trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating clinical trials unit (the Liverpool Clinical Trials Centre (LCTC) at the University of Liverpool) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator (CI), Professor Paul McNamara for the UK and Professor Anne Chang for Australia, via the LCTC.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 11.

Relationship Statements

Roles and responsibilities are fully described in section 14.

UK Sponsor: The University of Liverpool and will formally delegate specific sponsoring roles to the UK CI and LCTC, but remains legally responsible for the trial in the UK.

Australian Sponsor: Menzies School of Health Research and will formally delegate specific sponsoring roles to the Australian CI and LCTC, but remains legally responsible for the trial in the Australia.

Clinical Trials Unit: The LCTC at the University of Liverpool in collaboration with the UK and Australian CIs will have overall management responsibility for the trial from a clinical trials unit perspective and will be responsible for the co-ordination of centres.

The LCTC as part of the Liverpool Clinical Trials Collaborative has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as its standards and systems were assessed by an international review panel as reaching the highest quality. The LCTC has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and core standard operating procedures.

CONTACT DETAILS

Institutions

UK Sponsor:	**Australian Sponsor:**
University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: +44 (0) 151 794 8373 E-mail: sponsor@liverpool.ac.uk	Menzies School of Health Research John Mathews Building (Building 58) Royal Darwin Hospital Campus Rocklands Drive Casuarina NT 0810 Tel: +61 8 89468600
Trial Management, Monitoring and Analysis:	**Health Economics:**
Liverpool Clinical Trials Centre Institute in the Park Alder Hey Children's NHS Foundation Trust Eaton Road Liverpool L12 2AP Tel: +44 (0) 151 794 9838 E-mail: parrot@liverpool.ac.uk	Centre for Health Economics and Medicines Evaluation Ardudwy Hall Normal Site Bangor University Bangor Gwynedd LL57 2PZ Tel: +44 (0) 1248 382950 Email: d.a.hughes@bangor.ac.uk
Clinical Laboratory:	**Sleep Monitoring (Actigraphy):**
Menzies School of Health Research John Mathews Building Royal Darwin Hospital Campus Rocklands Drive TIWI NT 0810 Tel: +61 (08) 8946 8565 Email: anne.chang@menzies.edu.au	Activinsights 6 Nene Road, Bicton Industrial Park, Kimbolton, Cambridgeshire PE28 0LF Tel: +44 (0)1480 862 082 Email: info@activinsights.co.uk
UK Investigational Medicinal Product (IMP) Manufacturer and Suppliers:	**Australian IMP Manufacturer and Supplier:**
Royal Free Specials Pharmaceuticals Pond Street, London, NW3 2QG WGK Unit 3 Edison Close Park Farm Industrial Estate Wellingborough Northants NN8 6AH	PCI, PHARMACEUTICAL PACKAGING PROFESSIONALS PTY LTD 3/31 Sabre Drive, Port Melbourne Victoria, Australia 3207 Tel: +61 3 9673 1000 Email: Craig.rogers@pciservices.com

CONTACT DETAILS

UK Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**
Mr Alex Astor University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: +44 (0) 151 794 8373 E-mail: sponsor@liverpool.ac.uk	Professor Paul Stephen McNamara Consultant in Paediatric Respiratory Medicine, Alder Hey Children's NHS Foundation Trust Professor of Child Health, University of Liverpool Institute in The Park Alder Hey Children's Hospital Eaton Road Liverpool L12 2AP Tel: +44 (0)151 282 4531 Email: mcnamp@liverpool.ac.uk
Medical Expert who will Advise on Protocol Related Clinical Queries (if other than CI):	**Medical Expert who will Evaluate UK SAE Reports (if other than CI):**
Professor Calum Semple University of Liverpool Institute in The Park Alder Hey Children's Hospital Eaton Road Liverpool L12 2AP Tel: +44(0)151 252 5440 Email: m.g.semple@liverpool.ac.uk	Professor Calum Semple University of Liverpool Institute in The Park Alder Hey Children's Hospital Eaton Road Liverpool L12 2AP Tel: +44(0)151 252 5440 Email: m.g.semple@liverpool.ac.uk
Medical Expert who will Advise on Protocol Related Clinical Queries (if other than CI):	**Medical Expert who will Evaluate UK SAE Reports (if other than CI):**
Dr Michelle Heys Associate Professor and Consultant Paediatrician Great Ormond Street Institute of Child Health, UCL 30 Guildford Street London WC1N 1EH Tel: +44 (0)20 7905 2212 Email: m.heys@ucl.ac.uk	Dr Michelle Heys Associate Professor and Consultant Paediatrician Great Ormond Street Institute of Child Health, UCL 30 Guildford Street London WC1N 1EH Tel: +44 (0)20 7905 2212 Email: m.heys@ucl.ac.uk

CONTACT DETAILS

UK Individuals

Medical Expert who will Advise on Protocol Related Clinical Queries (if other than CI):	**Medical Expert who will Evaluate UK SAE Reports (if other than CI):**
Professor Jeremy Parr Professor of Paediatric Neurodisability Sir James Spence Institute Royal Victoria Infirmary Newcastle Upon Tyne NE1 4LP United Kingdom Telephone: +44 (0) 191 282 5966 Fax: +44 (0) 191 282 4725 Email: jeremy.parr@newcastle.ac.uk	Professor Jeremy Parr Professor of Paediatric Neurodisability Sir James Spence Institute Royal Victoria Infirmary Newcastle Upon Tyne NE1 4LP United Kingdom Telephone: +44 (0) 191 282 5966 Fax: +44 (0) 191 282 4725 Email: jeremy.parr@newcastle.ac.uk

CONTACT DETAILS:

Australian Individuals

Chief Investigator (CI) and Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	
Professor Anne Chang Menzies School of Health Research Charles Darwin University Rocklands Drive TIWI NT 0810 Tel: +61 (08) 8946 8565 Email: anne.chang@menzies.edu.au	
Medical Expert who will Advise on Protocol Related Clinical Queries (if other than CI):	**Medical Expert who will Evaluate Australian SAE Reports (if other than CI):**
Professor Dinah Reddihough The Royal Children's Hospital & Murdoch Children's Research Institute Flemington Road Parkville Victoria 3052 Australia Tel: +61 03 9345 5898 Email: dinah.reddihough@rch.org.au	Professor Dinah Reddihough The Royal Children's Hospital and Murdoch Children's Research Institute Flemington Road Parkville Victoria 3052 Australia Tel: +61 03 9345 5898 Email: dinah.reddihough@rch.org.au
Medical Expert who will Advise on Protocol Related Clinical Queries (if other than CI):	**Medical Expert who will Evaluate Australian SAE Reports (if other than CI):**
Professor Katrina Williams Monash Children's Hospital Level 5 246 Clayton Road Clayton VIC 3168 Tel: +61 3 857 23938 Email: katrina.williams@monash.edu	Professor Katrina Williams Monash Children's Hospital Level 5 246 Clayton Road Clayton VIC 3168 Tel: +61 3 857 23938 Email: katrina.williams@monash.edu

Additional Contacts:

The contact details of other individuals involved in the trial are detailed in documents supplementary to the protocol and stored in the Trial Master File (TMF):

Contact	Document Title
Trial Management Group (TMG) Trial Steering Committee (TSC) Independent Data and Safety Monitoring Committee (IDSMC)	PARROT Trial Oversight Committee Membership
Principal Investigators (PIs)	PARROT Participating Centres

TABLE OF CONTENTS

GLOSSARY

AE	Adverse Event
AMR	Antimicrobial Resistance
AR	Adverse Reaction
BACCH	British Association for Community Child Health
BACD	British Academy of Childhood Disability
BPRS	British Paediatric Respiratory Society
CA	Competent Authority
CF	Cystic Fibrosis
CHU9D	Child Health Utility Instrument
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CP	Cerebral Palsy
CRF	Case Report Form
CTIMP	Clinical Trials of an Investigational Medicinal Product
LCTC	Liverpool Clinical Trials Centre
EC	Ethics Committee
EOI	Expression of Interest
EUDRACT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
HEAP	Health Economics Analysis Plan
HES	Hospital Episode Statistics
hMPV	Human Metapneumovirus
HRA	Health Research Authority
HTA	Health Technology Assessment
HREC	Human Research Ethics Committee
ICER	Incremental Cost- Effectiveness Ratio
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
LRSQ	Liverpool Respiratory Symptom Questionnaire
LRTI	Lower Respiratory Tract Infection
MHRA	Medicines and Health Care Products Regulatory Agency
NI	Neurological Impairment
PI	Principal Investigator

PIC	Participant Identification Centre
PISC	Participant Information and Consent form
PLR	Personal Legal Representative
PPI	Patient and Public Involvement
PPR	Person with Parental Responsibility
QALY	Quality-Adjusted Life Years
QOL	Quality of Life
R&D	Research & Development
RCPCH	Royal College of Paediatrics and Child Health
REC	Research Ethics Committee
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
RSO	Research Support Office
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Coordinator
TGA	Therapeutic Goods Administration
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
USM	Urgent Safety Measure

1 PROTOCOL SUMMARY

Full Trial Title:	Joint UK and Australia multicentre, randomised, double blind, placebo controlled pragmatic trial comparing 52 weeks of azithromycin to placebo in children with neurological impairment at risk of lower respiratory tract infection.
Short Title:	Prophylactic antibiotics to prevent chest infections in children with neurological impairment (PARROT) trial.
Phase:	III
Target Condition:	Children and young persons with non-progressive neurological impairment (NI) and persistent respiratory symptoms at risk of hospitalisation for lower respiratory tract infections (LRTI).
Sample size:	500

Main Inclusion Criteria:

1. Children and young people who are aged between 3-17 years (inclusive) at randomisation
2. Written informed consent from participant (or appropriate person if incapacitated / minor)
3. Participant (or appropriate person if incapacitated / underage) and caregiver have a good understanding of the English language
4. Diagnosed with non-progressive, non-neuromuscular NI*
5. Persistent respiratory symptoms**
6. *One or more of the following:*
   - **a)** Received at least 2 courses of oral antibiotics for LRTI in 52 weeks prior to eligibility
   - **b)** Have been hospitalised with a LRTI within 52 weeks prior to eligibility and completed 13 week 'washout' period (where applicable)***
   - **c)** Prescribed prophylactic antibiotics for LRTIs and undergone a 13 week 'washout' period***

** Most will likely have cerebral palsy. However, some children may have no formal diagnosis to account for their symptoms.*

*** Defined by: LRSQ-Neuro score of ≥95% CI for age:*

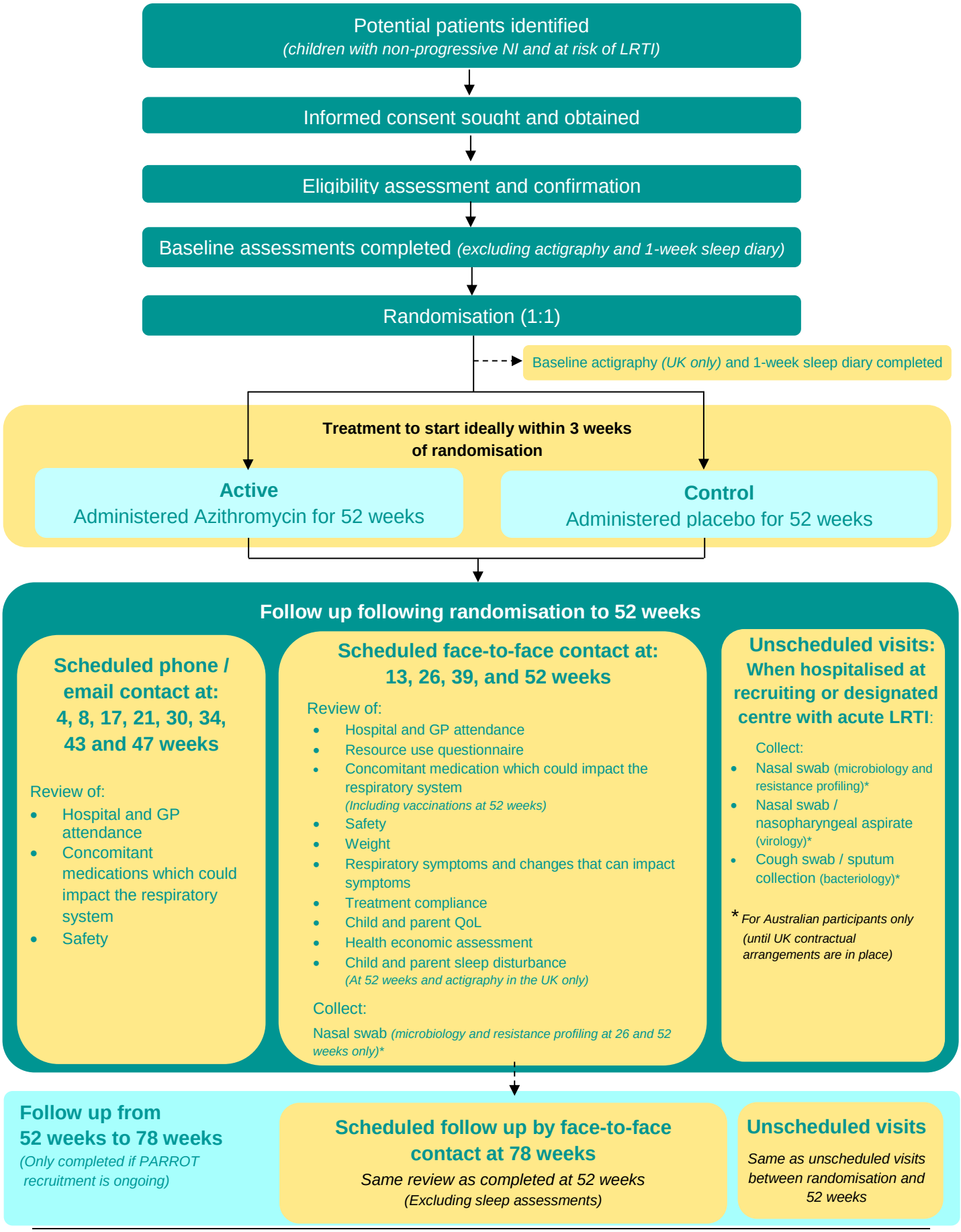
Age (in years)	LRSQ-Neuro total score
≥3 and <6	≥11
≥6 and <11	≥5
≥11 and ≤17	≥4

**** Must have undergone a 13 week 'washout' period where administered IV antibiotics during hospitalisation or have been previously prescribed and administered prophylactic or nebulised antibiotics. Before the washout period can take place, the paediatrician managing the patient's respiratory symptoms should be consulted to determine if there are any safety concerns at the point of considering enrolment which would prevent the patient from stopping prophylactic antibiotics.*

Main Exclusion Criteria:	**1.** Any neuromuscular disorders including SMA, Duchenne muscular dystrophy etc., or neurological disorders in which progressive deterioration in neurological condition are known to occur (e.g. Rett syndrome, some neurometabolic syndromes) **2.** Pre-existing non-neurological conditions that impact on respiratory function such as cystic fibrosis (CF), immunodeficiency etc. *Note: Children with NI known to have bronchiectasis will not be excluded.* **3.** Known contra-indication to using (e.g. prolonged QT syndrome) or hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic or to any of the excipients contained in the study drug **4.** Use of macrolide antibiotics within 90 days prior to eligibility **5.** Known significant hepatic disease (hepatic impairment per Child-Pugh classification C) **6.** Treatment with ergot derivatives (dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline or a combination of dihydroergocryptine with caffeine) **7.** Child/young person already taking prophylactic antibiotics for non-respiratory causes (e.g. UTIs). **8.** Previously randomised in PARROT **9.** Recruited to another IMP trial and continuing to administer the IMP
Trial Centres and Distribution:	Secondary and tertiary paediatric centres in the UK and large centres in Australia with associated clinical networks. Participant identification sources anticipated to include: - General paediatric, neurodevelopmental, neurodisability, community, neurology, paediatric rehabilitation, respiratory or specialist neuro-respiratory clinics, including those delivered through education and community settings - Inpatient hospital admissions with LRTI - Advertisement in outpatient clinics / hospices / respite care facilities, community-based special needs schools, parent carer forums, consumer organisations, via social media, through the PARROT website or via links from charity websites - Contact through local paediatricians and specialist neurodevelopmental paediatricians

Participant Trial Duration:	Randomised patients will receive 52 weeks of treatment with either: • Azithromycin or; • Placebo. All participants will be followed up for 52 weeks from randomisation. If trial recruitment is ongoing at 78 weeks, participants will also be followed up at this time point.
Overall Trial Duration:	Trial recruitment and follow up duration: 4 years Full trial funding (including final report): 5 years The trial will incorporate an internal pilot phase (see section 3 for more details).
Description of Intervention:	**Intervention:** Powder formulation of Azithromycin reconstituted and administered as an oral suspension. The dosing regimen will be based on body weight (10mg/kg rounded) and will be given 3x/week (Mon/Wed/Fri). **Control:** Matched reconstituted powder formulation of placebo.
Primary Objective:	To determine whether 52 weeks of azithromycin prophylaxis is more effective than placebo in reducing the proportion of children with non-progressive NI admitted to hospital with LRTI.
Secondary Objectives:	1. To determine if 52 weeks of antibiotic prophylaxis with azithromycin compared to placebo improves: i. Parent reported health-related Quality of Life (QoL) for both parent and child/young person ii. Child / young person nutritional status iii. Amount and quality of sleep for both parent and child / young person iv. Child / young person LRSQ-Neuro score 2. To estimate the cost-effectiveness of prophylactic azithromycin based on: i. Resource use and costs associated with 52 weeks of antibiotic prophylaxis with azithromycin ii. Number of quality-adjusted life years (QALYs) experienced 3. To compare respiratory tract microbiology and specifically rates of antimicrobial resistance (AMR) 4. To determine the point prevalence of respiratory viral and bacterial detection for respiratory related hospitalisations. 5. To assess residual impact of 52 weeks antibiotic prophylaxis at 78 weeks.

Schematic of Trial Design



2 INTRODUCTION

2.1 Background

Improvements in neonatal and paediatric care in recent decades have resulted in the survival of increasing numbers of children with non-progressive multiple and profound NI. Many of these children have cerebral palsy (CP), the commonest childhood physical disability. In high income countries the overall incidence of CP is 2.0-2.5/1000 live births, and severe CP (GMFCS VI-V) occurs following 0.4/1000 live births(1). By 2020, it is estimated the number of children aged 0-15 years living with CP in England & Wales will be 27,441(2). While these figures provide a guide, they underestimate the number of children with NI as there are many causes for NI other than CP.

Respiratory symptoms in children with NI are common and often have many causes (Figure 1), making them very difficult to manage. Lower respiratory tract infection (LRTI), frequently occurs causing repeated and lengthy hospitalisations, bronchiectasis and premature death(3-5). The impact of these hospital admissions on health service expenditure is significant and places a huge burden on children, their families and healthcare services(6, 7). A review of US paediatric hospital admissions in 2006 found that 29% of US children's hospital expenditure was on inpatient care of children with NI, with >10% of these admissions being for respiratory tract infection(8). Using NHS England data, we have estimated that the total cost for hospital management of LRTI in children with NI (HRG Currency Codes PD14A, B &C) was more than £32m in 2015/16.

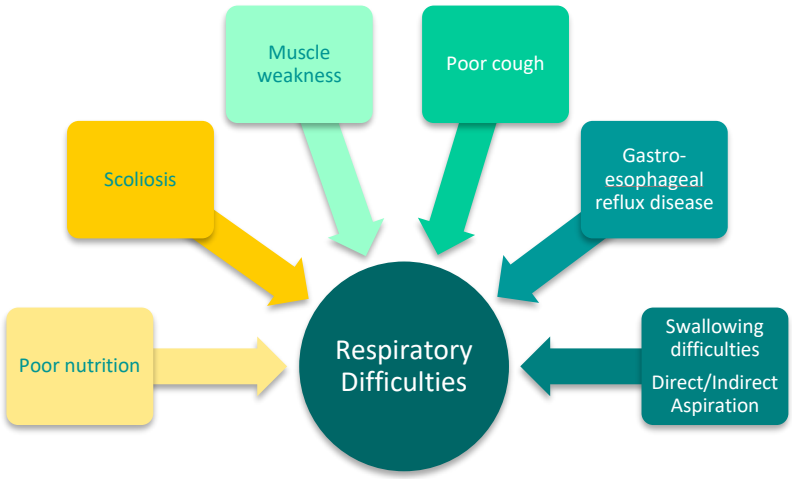


Figure 1: Aetiology of respiratory disease in children with NI

2.2 Rationale

Chest symptoms and infections are a common concern for parents of children with NI and clinicians alike. To reduce these symptoms, prophylactic antibiotics are sometimes used(9, 10), but the type of antibiotic, duration and dose often vary considerably. Furthermore, these medications are not without side-effects, and there are concerns about risks associated with their long-term use, particularly regarding the development of antimicrobial resistance(11). A Cochrane review has highlighted the lack of evidence supporting their use in this group of patients and recommended that further research in this area is needed(12), hence this trial.

Children with NI often start prophylaxis if they have persistent respiratory symptoms requiring regular courses of antibiotics or if they have admissions to hospital with chest infections. In the UK, Azithromycin is one of several antibiotics used in this situation. This antibiotic has been chosen for this trial because it has proven efficacy in the prevention and treatment of severe LRTI, having been found to reduce respiratory exacerbations and hospitalisation in children with bronchiectasis(13, 14). As well as antibacterial properties against common causes of LRTI, it also has potential anti-inflammatory effects and reduces virulence factors like biofilm production in intrinsically resistant bacteria such as Pseudomonas aeruginosa, an organism commonly found in respiratory tract secretions from children with NI(15). Azithromycin also comes as a suspension and importantly only needs to be given three times per week(13, 16, 17).

As part of feasibility work for this trial, parents of children with NI were asked what they thought were the most important outcomes related to antibiotic prophylaxis. They said that the most important measure for them was rate of hospitalisation. Consequently, the primary outcome for this trial will be to confirm whether prophylactic antibiotics (azithromycin) significantly alters the rates of hospital admission due to LRTI in children with NI compared to those given placebo. We have based the sample size calculation for this trial on a 30% reduction in hospital admissions.

Another important outcome measure mentioned by parents was respiratory symptoms. Unfortunately, there are no formally validated respiratory symptom questionnaires for children with NI and so this trial will use a modified instrument that has been used previously(18). The Liverpool Respiratory Symptom Questionnaire (LRSQ) was developed for pre-school children with respiratory symptoms and CF(19, 20). It uses Likert scales, comprises 8 domains (see Section 7.4.1), takes <10 minutes to complete and elicits symptoms over a three-month period. For children with NI, the questionnaire has been modified by removing 'activity' domain/questions, resulting in the 'LRSQ-Neuro'. Working with parents and healthcare professionals in both the UK and Australia as part of the preparation for this trial, a bespoke questionnaire to be completed by parents of children with NI has also been designed. This will undergo further validation during the PARROT trial.

Other important measures identified by parents and healthcare professionals included assessing whether antibiotic prophylaxis is cost effective, reduces healthcare utilisation and improves health-related QoL and sleep (for both parents and children/young people), whilst not adversely influencing respiratory tract microbiology or causing adverse events/side effects. These have all been included as secondary outcome measures in PARROT.

There is very little information as to the infective causes of LRTI in children with NI(21). This trial will examine bacterial and viral causes of LRTI in this patient group. In future, this information may be invaluable as new antivirals against common respiratory viral pathogens such as RSV, hMPV and PIV are in early phase clinical trials.

Overall, more evidence of the clinical and cost-effectiveness of using prophylactic antibiotics will allow parents, clinicians and health services to incorporate risks and benefits into their decision making. Availability of high-quality evidence will result in management guidelines, which when implemented, might lead to reduction in exacerbations, hospitalisations and health costs and improved QoL.

2.3 Risk and Benefits

Azithromycin is used widely for the treatment of childhood infection with very few side effects, though some children and young persons may experience mild diarrhoea, stomach pains, nausea or vomiting when they first start taking azithromycin. Other side effects include headache and feeling dizzy. There is a small chance that azithromycin may cause a rash, or hearing problems. The development of microbial resistance will be reviewed during the trial.

Children and young persons randomised and administered to azithromycin may benefit from a reduction in the development of LRTI and improved parent reported respiratory symptoms (LRSQ score).

Children and young persons already receiving prophylactic antibiotics, who want to participate, will have to stop their antibiotics 13 weeks before randomisation to either azithromycin / placebo – the 'wash-out' period. It is possible that during this period they could become more symptomatic or that a respiratory exacerbation could be precipitated. To reduce this risk, families will be given the option to delay trial enrolment to the summer months when there will be less risk of developing chest infections.

Due to the varied use of prophylactic antibiotic treatment as standard care and consequently the design of PARROT, there is no bigger risk to taking part in this trial than with standard care. Parents will be fully informed by their local delegated PARROT researcher as to these potential risks.

In this trial, face-to-face appointments have been kept to a minimum to minimise the burdens of trial participation as far as possible. Furthermore, we will try to arrange for these to be with existing hospital appointments. Feasibility investigations have suggested that parents value monthly contact; parents will be given options as to how this contact will occur (phone / email) to further minimise the burden of participation.

2.4 Objectives and Outcome Measures

2.4.1 Primary Objective and Outcome Measures

Primary Objective	Primary Outcome Measure	Time point(s) of evaluation of this outcome measure
To determine whether 52 weeks of azithromycin prophylaxis is more effective than placebo in reducing the proportion of children with non-progressive NI admitted to hospital with LRTI.	Proportion of children hospitalised* with LRTI over the 52-week intervention period	At 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks: • Hospitalisations at recruiting or designated centre due to LRTI (according to below definition) *Note: Outcome assessment will be at 52 weeks.*

There are no existing published definitions for what comprises a lower respiratory tract infection in this patient group. For the purposes of this trial, LRTI has been defined for children with NI based on existing definitions for children without NI(13, 22) combined with some symptoms and signs considered pertinent to this group of patients by the PARROT investigatory team. Thus, for a diagnosis of LRTI to be made, whether necessitating hospitalisation or not, a child with NI must have two or more of the following over a **48-hour period** (based on clinical judgement and age related definitions unless specified):

- Increased secretion volume/viscosity of respiratory secretions
- Change in temperature by 1°C **or** lethargy/fatigue
- Increased cough
- Increased work of breathing (tachypnoea or dyspnoea)
- Increased oxygen requirement
- Increased need for respiratory support (such as increased chest physio/suction/cough assist)
- Changes on chest X-ray or chest auscultation

*Hospitalisation includes those who are admitted to hospital for only a short period with LRTI e.g. 12 hours and go home with a course of antibiotics. However, if participants are hospitalised again within 2 weeks of the initial admission, this will be classified as the same event.

2.4.2 Secondary Objectives and Outcome Measures

Secondary Objectives	Secondary Outcome Measures	Time point(s) and method of evaluation of this outcome measure (if applicable)
1. To determine if 52 weeks of antibiotic prophylaxis with azithromycin compared to placebo improves: i. Parent reported health-related QoL for both parent and child/young person	Change in health related QoL of child and parent / carer	At baseline, 13, 26, 39 and 52 weeks • Parent QoL assessment (Warwick-Edinburgh Mental Wellbeing Scale) • Patient QoL assessment (DISABKIDS)
	Safety events, tolerability and adherence	At 4, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks: • Assessment of adverse events • Withdrawals from study treatment At 13, 26, 39 and 52 weeks: • IMP treatment diary
	Changes in respiratory medication usage (i.e. 'stepping down' asthma treatment, decreasing chest physiotherapy frequency or use of cough-assist etc.)	At baseline, 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks: • Review of concomitant medication which could impact the respiratory system At baseline and 52 weeks: • Vaccinations

Secondary Objectives	Secondary Outcome Measures	Time point(s) and method of evaluation of this outcome measure (if applicable)
ii. Child / young person nutritional status	Changes in weight based on World Health Organisation z-scores using WHO Anthro (3.2.2) calculator (https://www.who.int/growthref/tools/en/)	At baseline, 13, 26, 39 and 52 weeks: • Weight
iii. Amount and quality of sleep for both parent and child / young person	Change in quality / amount of parent and child / young person's sleep	At baseline and 52 weeks: • Primary caregiver sleep actigraphy and corresponding primary caregiver sleep log (UK only) • Child's Sleep Habits Questionnaire • 1 week patient sleep diary
iv. Child / young person respiratory symptoms	Change in respiratory symptoms	At baseline, 13, 26, 39 and 52 weeks: • LRSQ-Neuro score • Respiratory symptom questionnaire At 13, 26, 39 and 52 weeks: • Changes to respiratory treatments / support • Surgical and other interventions
2. To estimate the cost-effectiveness of prophylactic azithromycin based on:		
i. Resource use and costs associated with 52 weeks of	Number, duration and severity of LRTI; time to first LRTI	At 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks:

Secondary Objectives	Secondary Outcome Measures	Time point(s) and method of evaluation of this outcome measure (if applicable)
antibiotic prophylaxis with azithromycin		• Chest infection and LRTI Changes to respiratory treatments / support • Assessment of adverse events At baseline, 13, 26, 39 and 52 weeks: • Resource use questionnaire Unscheduled follow-up: • Length of stay in hospital • Admission to PICU/HDU • Changes to respiratory treatments / support
	Unscheduled medical presentations (GP visits and A&E attendances) for LRTI *Note: The LRTI definition at GPs will vary to the primary endpoint definition of LRTI*	At baseline weeks: • Medical history review At 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks: • Chest infection and LRTI • Assessment of adverse events At baseline, 13, 26, 39 and 52 weeks: • Resource use questionnaire
	Use of other health and social care services, school attendance and indirect costs	At baseline, 13, 26, 39 and 52 weeks: • Resource use questionnaire For participants that attend English centres at 52 weeks:

Secondary Objectives	Secondary Outcome Measures	Time point(s) and method of evaluation of this outcome measure (if applicable)
ii. Number of quality-adjusted life years (QALYs) experienced		• Hospital Episode Statistics (HES)
	Number of courses of 'rescue' antibiotics prescribed for LRTI	At baseline, 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks: • Review of concomitant medications which could impact the respiratory system
	Quality-adjusted life years (QALY) assessment	At baseline, 13, 26, 39 and 52 weeks: • CHU9D and EQ-5D-Y
3. To compare respiratory tract microbiology and specifically rates of AMR*	Nasal swab microbiology and resistance profiling	At baseline, 26 and 52 weeks, and for unscheduled visits: • Nasal swab
4. To determine the point prevalence of respiratory viral and bacterial detection for respiratory related hospitalisations*	Nasal swab/nasopharyngeal aspirate to investigate viral causes of acute LRTI** Cough swab/sputum collection to investigate bacterial causes of acute LRTI**	When / if children are hospitalised at their recruiting or designated centre with acute LRTI: • Nasal swab / nasopharyngeal aspirate and a cough swab / sputum collection
5. To assess residual impact of 52 weeks antibiotic prophylaxis at 78 weeks	Change in respiratory symptoms	At 78 weeks***: • LRSQ-Neuro score • Respiratory symptom questionnaire • Changes to respiratory treatments / support • Surgical and other interventions

Secondary Objectives	Secondary Outcome Measures	Time point(s) and method of evaluation of this outcome measure (if applicable)
	Changes in weight based on World Health Organisation z-scores using WHO Anthro (3.2.2) calculator (https://www.who.int/growthref/tools/en/)	At 78 weeks***: • Weight
	Nasal swab microbiology and resistance profiling	At 78 weeks***: • Nasal swab (microbiology and resistance profiling)
	Changes in respiratory medication usage (i.e. 'stepping down' asthma treatment, decreasing chest physiotherapy frequency or use of cough-assist etc.)	At 78 weeks***: • Review of concomitant medications which could impact the respiratory system • Review of vaccinations
	Number, duration and severity of LRTI; time to first LRTI	At 78 weeks***: • Resource use questionnaire • Chest infection and LRTI • Changes to respiratory treatments / support • Collection of adverse events
	Quality-adjusted life years (QALY) assessment	At 78 weeks***: • Health economic outcomes (CHU9D and EQ-5D-Y)
	Use of other health and social care services, school attendance and indirect costs	At 78 weeks***: • Hospital Episode Statistics (HES)

Secondary Objectives	Secondary Outcome Measures	Time point(s) and method of evaluation of this outcome measure (if applicable)
	Change in health related QoL of child and parent / carer	At 78 weeks***: • Patient QoL assessment (DISABKIDS) • Parent QoL assessment (Warwick-Edinburgh Mental Well-being Scale)
	Unscheduled medical presentations (GP visits and A&E attendances) for LRTI *Note: The LRTI definition at GPs will vary to the primary endpoint definition of LRTI*	At 78 weeks***: • Chest infection and LRTI • Collection of adverse events • Resource use questionnaire
	Number of courses of 'rescue' antibiotics prescribed for LRTI	At 78 weeks***: • Review of concomitant medications which could impact the respiratory system
	Safety events	At 78 weeks***: • Assessment of adverse events

** For Australian participants only (until UK contractual arrangements are in place)*
*** LRTI as defined for the primary outcome in section 2.3.1*
****78-week outcome measures will only be completed if PARROT recruitment is ongoing.*

3 TRIAL DESIGN

PARROT will be a joint UK and Australian multicentre trial with patients randomised to either 52 weeks prophylactic azithromycin or placebo in a 1:1 ratio. Both patients and their healthcare teams will be blinded to treatment allocation.

3.1 Internal Pilot

The trial will incorporate an internal pilot phase with criteria for continuation to a full trial. The criteria are as follows:

I. Consent rate

- ≥50%, then proceed to main trial.
- ≥25-49%, then the reasons why patients / their families do not want to participate will be investigated to identify any aspects amenable to change. We will liaise with our Patient and Public Involvement group to explore methods to increase recruitment rates.
- < 25%, we will analyse reasons why patients do not want to participate. If consent declination cannot be improved then we will abandon the main trial.

II. Completed Data

- ≥90%, then proceed to main trial.
- ≥60-89%, analyse reasons for missing data and identify whether any aspects are amenable to change. Then proceed to main trial as amended.
- <60%, then abandon plan for main trial.

III. Recruitment

- If, based on the recruitment achieved in the internal pilot, the predicted total recruitment period is 36 months or less, proceed to main trial.
- If the predicted recruitment period is more than 36 months, consider and introduce ways to reduce this e.g. increase the number of trial centres, determine whether local centre training needs are being met, or whether any new evidence suggests that eligibility criteria could be widened. Then proceed to main trial as amended.

3.2 Patient and Public Involvement (PPI)

Parents of children with neurological impairment were involved in all stages in the development of this trial from its conception. PPI informed the recruitment strategy, inclusion and exclusion criteria and added to the outcomes of the trial. Parent advisors will continue to have a crucial role in ensuring the trial addresses the needs and concerns of families of children with neurological impairment, and information from the trial is made available in formats they find useful.

The PPI Terms of Reference will be used to confirm activity throughout the trial and will report PPI using GRIPP2 Short Form reporting guidance.

4 TRIAL SETTING AND SELECTION OF CENTRES / CLINICIANS

PARROT will recruit from secondary and tertiary paediatric centres in the UK and Australia. It is anticipated that approximately 40 centres will be involved, of which 3 will be paediatric centres in Australia with associated clinical networks (Brisbane, Darwin and Melbourne).

Criteria for the selection of UK centres will be determined by the Trial Management Group (TMG) and will be described in the supplementary document 'PARROT Centre Assessment Criteria'.

Selected centres will be opened to recruitment upon:

- successful completion of all global and local conditions (e.g. Ethics Committee (EC) and Competent Authority (CA) approvals);
- trial-specific conditions (e.g. centre personnel training requirements) and;
- once all necessary documents have been returned to LCTC as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in the 'PARROT Participating Centres' log, maintained separately to the protocol and stored in the TMF.

5 TRIAL POPULATION

5.1 Inclusion Criteria

1. Children and young people who are aged between 3-17 years (inclusive) at randomisation
2. Written informed consent from participant (or appropriate person if incapacitated / minor)
3. Participant (or appropriate person if incapacitated / underage) and caregiver have a good understanding of the English language
4. Diagnosed with non-progressive, non-neuromuscular NI*
5. Persistent respiratory symptoms**
6. *One or more of the following:*
   - **a)** Received at least 2 courses of oral antibiotics for LRTI in 52 weeks prior to eligibility
   - **b)** Have been hospitalised with a LRTI within 52 weeks prior to eligibility and completed 13 week 'washout' period (where applicable)***
   - **c)** Prescribed prophylactic antibiotics for LRTIs and undergone a 13 week 'washout' period***.

* Most will likely have cerebral palsy. However, some children may have no formal diagnosis to account for their symptoms.
** Persistent respiratory symptoms defined by LRSQ-Neuro score of ≥95%CI for age, i.e.:

Age (in years)	LRSQ-Neuro total score
≥3 and <6	≥11
≥6 and <11	≥5
≥11 and ≤17	≥4

*** Must have undergone a 13 week 'washout' period where administered IV antibiotics during hospitalisation or have been previously prescribed and administered prophylactic or nebulised antibiotics. Before the washout period can take place, the paediatrician managing the patient's respiratory symptoms should be consulted to determine if there are any safety concerns at the point of considering enrolment which would prevent the patient from stopping prophylactic antibiotics.

5.2 Exclusion Criteria

1. Any neuromuscular disorders including SMA, Duchenne muscular dystrophy etc., or neurological disorders in which progressive deterioration in neurological condition are known to occur (e.g. Rett syndrome, some neurometabolic syndromes)
2. Pre-existing non-neurological conditions that impact respiratory functions such as CF, immunodeficiency etc.
   Note: Children with NI known to have bronchiectasis will not be excluded.
3. Known contra-indication to using (e.g. prolonged QT syndrome) or hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients contained in the study drug
4. Use of macrolide antibiotics within 90 days prior to eligibility
5. Known significant hepatic disease (hepatic impairment per Child-Pugh classification C)

6. Treatment with ergot derivatives (dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline or a combination of dihydroergocryptine with caffeine)
7. Child / young person already taking prophylactic antibiotics for non-respiratory causes (e.g. UTIs)
8. Previously randomised in PARROT
9. Recruited to another IMP trial and continuing to administer the IMP.

5.3 Co-enrolment Guidelines

To avoid potentially confounding issues, patients must not be recruited to PARROT if they are participating in another IMP trial. Ideally patients should not be recruited to any other trials whilst they are participating in PARROT. However, where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the PARROT trial, this must first be discussed with the LCTC who will contact the CI in the UK or Australia as required.

6 RECRUITMENT AND RANDOMISATION

6.1 Participant Identification and Screening

6.1.1 Participant Identification

Identification of potential participants will vary across recruitment centres and Participant Identification Centres (PICs) may be used where necessary.

Identification could be through one or a combination of but not exclusive to, the following methods:

- Clinics (including those held in education or community settings):
  - General paediatric;
  - neurodevelopmental;
  - neurodisability;
  - community;
  - neurology;
  - paediatric rehabilitation;
  - respiratory or;
  - specialist neuro-respiratory.
- Inpatient hospital admissions with LRTI.
- Advertisement:
  - in outpatient clinics / hospices / respite care facilities;
  - community-based special needs schools;
  - Parent carer forums;
  - Consumer organisations;
  - via social media;
  - through the PARROT website or;
  - via links from charity websites.
- Contact through local paediatricians and specialist neurodevelopmental paediatricians.

Posters and information sheets will be available to aid identification and advertisement with links to the PARROT website to allow identification of local PARROT centres and teams. PICs sites will not be able to forward any potential participant details to the recruiting centres.

Additional posters and information sheets will also be available and will provide the contact details of the local delegated research team who can provide further information to potential participants.

6.1.2 Initial Screening

A delegated member of the research team must start the completion of the screening log to confirm identification of a potentially eligible patient if they are:

- Aged between 3-17 years (inclusive) at randomisation;
- Diagnosed with non-progressive, non-muscular NI* and;
- Participant (or appropriate person if incapacitated / underage) and caregiver have a good understanding of the English language
- One or more of the following:
  a) Received at least 2 courses of oral antibiotics for LRTI in 52 weeks prior to eligibility
  b) Have been hospitalised with a LRTI within 52 weeks prior to eligibility and completed 13 week ‘washout’ period (where applicable)

c) Prescribed prophylactic antibiotics for LRTIs and completed 13 week 'washout' period

At this stage, if the patient fulfils the above but it is known that the patient does not fulfil the remaining eligibility criteria, then the reasons that the patient is ineligible should be recorded on the screening log.

** Most will likely have cerebral palsy. However, some children may have no formal diagnosis to account for their symptoms.*

Only once written informed consent has been provided can:

- any trial specific procedures be completed or;
- the research team (who are outside the direct clinical care) access the patient's medical notes.

Therefore, for example, the LRSQ-Neuro score cannot be obtained and a full assessment of eligibility, be completed until after written informed consent has been provided.

6.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the researcher should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

6.2.1 Informed Consent from Participants

Due to the patient population, it is expected that most participants will not be able to provide written informed consent for themselves due to their age and / or capacity.

For minors, informed consent will be sought from a person with parental responsibility (PPR).
For adults without capacity, informed consent will be sought from a personal legal representative (PLR).
For adults with capacity, the patient must consent for themselves and their caregiver be provided with the caregiver information leaflet which details how they will assist with the research.
The legal framework for each recruiting centre should be followed for the definitions of adults and minors when consenting to research.

Where possible, the trial will be introduced to the patient / PPR / PLR by familiar members of the usual clinical care team. If the patient / PPR / PLR is interested, a member of the usual care team can then make an introduction to the research team. Members of the research team must be appropriately trained, qualified and be delegated to seek informed consent prior to participating in any consent discussions.

Discussion of objectives, treatment options, including the conventional and generally accepted methods of treatment, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided by a member of the delegated research team. The applicable Participant Information and Consent form(s) (PISCs), describing in detail the trial interventions, trial procedures and risks will also be provided.

The patient / PPR / PLR (as applicable) will be asked to read and review the applicable PISC. Upon reviewing the document, the researcher will explain the trial further to the patient / PPR / PLR. This information will emphasise that participation in the trial is voluntary and that the patient / PPR / PLR may withdraw from the trial at any time and for any reason. The rights and welfare of the patients will be

protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in the trial.

The patient / PPR / PLR will be given opportunity to ask any questions that may arise, have the opportunity to discuss the trial with their surrogates and, whilst recruitment is ongoing, will have as long as is required to decide whether they wish to be involved. A contact point where further information about the trial may be obtained will be provided.

If the patient / PPR / PLR would like to take part, then they will sign and date the PISC. Both the person seeking consent and the patient / PPR / PLR must personally sign and date the form. The original wet-ink copy will be filed in the Investigator Site file. Copies will be: given to the patient / PPR / PLR for their records, filed in the patient's notes and sent to the LCTC.

After the patient has entered the trial, the clinician will remain free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the patient. Similarly, the patient / PPR / PLR remains free to withdraw the patient / themselves at any time from the protocol treatment, trial follow-up and any samples held for future research without giving reasons and without prejudicing the further treatment (see section 7.6 for further details on withdrawals).

6.2.2 Assent from Patients

Due to the trial population, most potential patients are not expected to have the capacity to provide written assent. However, in the UK if a patient is aged 6 years or over, sites must assess if the child has capacity to assent.

If capacity allows, there are two information leaflets and an assent form:-

- Capacity 1 (C1): this is aimed at 6 – 11 year olds;
- Capacity 2 (C2): this is aimed at 12-15 year olds, however the C1 information leaflet may be used instead if it is more appropriate for the patient's level of capacity.

The outcome should be recorded accordingly on the assent form: patient assents, declines assent, prefers not to make a decision. If the participant is aged between 6 and 15 years old but does not have the appropriate level of development capacity to assent then this will be documented on the assent form.

For both the UK and Australia, a patient key information sheet can be provided to the patient (and/or their family) where appropriate to help explain the trial in simplified terms. The patient key information sheet can also be provided to participants who do not have the capacity to assent or are under 6 years old (where appropriate).

6.2.3 Consent for Hospital Episode Statistics

For UK participants only
If the patient / PPR / PLR, who would provide informed consent, does not provide agreement to use HES then this will not exclude the patient from the main trial.

6.2.4 Consent for Sleep Actigraphy

For UK participants only

Only the patient's primary caregiver, can complete the sleep actigraphy and the associated primary caregiver sleep log. If the primary caregiver does not wish to take part in the sleep actigraphy then this will not exclude the patient from the main trial.

6.3 Eligibility

Only once written informed consent has been provided (see section 6.2) can all eligibility criteria be assessed, including assessing the patient's LRSQ-Neuro score for persistent respiratory symptoms (see section 7.4.1). Eligibility criteria can be assessed by a member of the research team who is delegated to do so.

However, only a delegated and licenced medical practitioner can confirm eligibility and this must be completed prior to baseline assessments (see section 6.4) and randomisation (see section 6.5).

Assessment and confirmation of the patient's eligibility should be recorded in the patient's notes and on the screening log which is returned to LCTC.

6.4 Baseline Assessments

All baseline assessments must be completed:

- only once patient eligibility has been confirmed (see section 6.3);
- prior to randomisation (excluding sleep actigraphy and 1 week patient sleep diary) and;
- prior to commencing trial treatment (trial treatment to start ideally within 3 weeks of randomisation).

6.4.1 Baseline Assessments completed by research team

A delegated member of the research team must complete the following baseline assessments:

- Weight
- Nasal swab (microbiology and resistance profiling)*
- Concomitant medication that could impact the respiratory systems (including, for example, anti-reflux medications)
- Vaccinations within the last 52 weeks**
- Recent medical history: emergency hospital attendances in the last year associated with LRTI**
- Recent medical history: GP attendances in the last year associated with LRTI**

** For Australian participants only (until UK contractual arrangements are in place).*
***Discussed and obtained from patient / caregiver if required.*

6.4.2 Baseline Assessments completed by the Patient / Caregiver

The caregiver must complete the following baseline assessments:

- Respiratory symptom questionnaire
- Resource use questionnaire
- Warwick-Edinburgh Mental Wellbeing Scale
- Child's Sleep Habits Questionnaire
- 1 week patient sleep diary

- DISABKIDS (Proxy completion)
- EQ-5D-Y (Proxy completion)
- CHU9D (Proxy completion)

If capacity allows the patient must also complete the following questionnaires:

- DISABKIDS
- EQ-5D-Y
- CHU9D

For UK participants:
If the caregiver is completing the sleep actigraphy assessment, this must be completedafter randomisation but prior to treatment administration (see section 7.4.6).

6.5 Randomisation

A delegated and licenced medical practitioner must confirm eligibility prior to commencement of any baseline assessments and randomisation completion. Randomisation can take place during the same visit when written consent is provided but must be completed within 2 weeks of informed consent being obtained.

Patients will be randomised to receive either prophylactic azithromycin or placebo (in a ratio of 1:1). Treatment administration should ideally start within 3 weeks of randomisation once all baseline assessments have been completed (including patient and caregiver sleep assessments).

Once the patient has been randomised and if the applicable permissions are in place, a member of the local research team will enter the following information into the LCTC contact database:-

- For HES data (if optional consent is provided): Patient details including postcode, date of birth, NHS number, trial randomisation identifier and gender to enable the collection of HES data
- For actigraphy (if caregiver confirms they wish to assist with the research): Caregiver contact details including name, address and telephone details to enable Activinsights to provide the actigraphy watch.

6.5.1 Electronic Randomisation

Participants will be randomised using a secure (24-hour) web-based randomisation programme controlled centrally by the LCTC. A personal login username and password, provided by the LCTC, will be required to access the randomisation system; designated research staff will be issued with their personal login and password upon completion of training in the use of the system and once delegated for randomisation on the trial delegation log.

When the system requirements (consent and, eligibility) are confirmeda unique trial number (randomisation number) will be displayed on a secure webpage and an automated email confirmation will be sent to the delegated unblinded team (usually pharmacy) to confirm treatment allocation. The centre's PI, LCTC Trial Coordinator (TC) and the research staff member responsible for randomisation will receive a separate email confirming that randomisation has taken place without revealing treatment allocation. It is the responsibility of the PI or delegated research staff to inform the pharmacy

department/dispensing facility at their centre prior to randomisation to ensure there is sufficient supply of the trial treatments.

Randomisation: web access
https://ctrc.liv.ac.uk/Randomisation/Parrot

If there are any problems with the randomisation systems contact the LCTC on 0151 794 9838 or via email on parrot@liverpool.ac.uk

(Note that the LCTC is open from 0900 – 1700 (GMT), Monday – Friday, excluding English public holidays)

6.5.2 Randomisation system failure

The delegated unblinded team at recruiting centres will be provided with emergency back-up randomisation envelopes to be used in the event of a failure occurs outside LCTC office hours or if the problem cannot be resolved in a reasonable timeframe.

In the event that emergency back-up envelopes are required, the randomising person will contact a member of the unblinding team who will randomise the patient. They will select the next sequentially numbered, opaque, pressure-sealed envelope that will give the randomised allocation. The envelope will be similar to those used for pay slips, which cannot be viewed without fully opening and their construction is resistant to accidental damage or tampering. Page 1 of the randomisation envelope containing information on the allocation should be returned to the unblinded PARROT team at LCTC in a pre-paid envelope, and pages 2 & 3 of the randomisation envelope can be inserted into the patient's medical records. The centre should also email the TC within 24 hours to notify LCTC that it has been necessary to use a back-up envelope.

A delegated researcher will check regularly to ensure that the correct number of randomisation envelopes are present, that they are intact and that the sequential numbering system is maintained. Any discrepancies should be immediately reported to the LCTC.

6.5.3 Contact database failure

In the event that the contact database is unavailable, the local research team will be required to record the applicable contact information in the patient notes. As soon as the issue with the system is resolved, site will be asked to enter the information into the database.

6.6 Who is Blinded to Allocations

PARROT is a double-blind trial so patients and their research / treating clinical team will be blinded to treatment allocation. However, at each centre there will be a designated unblinding team (usually pharmacy), who will be unblinded to treatment allocations. The unblinded team will not be involved in patient care apart from dispensing their treatment. For unblinding procedures see section 8.4.

7 PARTICIPANT TIME LINE, ASSESSMENTS AND PROCEDURES

7.1 Administration of Intervention

As PARROT is a double-blinded trial, patients and their medical team will not know if a patient is receiving azithromycin or placebo. Following randomisation, the trial intervention will be dispensed. The trial intervention must be started after the baseline sleep assessments have been completed (where applicable) and should ideally be within 3 weeks of randomisation. Administration will be at home by the patient, parent or carer (see Section 9 for more information) and for 52 weeks. In selected circumstances in Australia, supervised dosing may be used.

7.2 Schedule for Follow-up

Assessment	Screening / randomisation	Baseline	Follow up *(in weeks)*													
			4[3]	8[3]	13	17[3]	21[3]	26	30[3]	34[3]	39	43[3]	47[3]	52	78[4]	Unscheduled visit[5]
Informed consent	X															
Medical history review	X	X														
LRSQ-Neuro	X				X			X			X			X	X	
Confirmation of eligibility criteria[1]	X															
Randomisation	X															
Dispense trial intervention		X			X			X			X					
Administration of trial intervention[2]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Return completed IMP treatment diary					X			X			X			X		
Weight		X			X			X			X			X	X	
Respiratory symptom questionnaire		X			X			X			X			X	X	
Nasal swab (microbiology and resistance profiling)[6]		X						X						X	X	X
Cough swab / sputum collection (bacteriology)[6]																X
Nasal swab/nasopharyngeal aspirate (virology)[6]																X
Review of concomitant medications which could impact the respiratory system		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of vaccinations		X												X	X	
Changes to respiratory treatments / support			X	X	X	X	X	X	X	X	X	X	X	X	X	
Surgical and other interventions					X			X			X			X	X	
Review of GP, A&E attendances and hospital admissions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Resource use questionnaire		X			X			X			X			X	X	
Collection of adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient/Proxy QoL assessment *(DISABKIDS)*		X			X			X			X			X	X	
Caregiver QoL assessment *(Warwick-Edinburgh Mental Wellbeing*		X			X			X			X			X	X	
Patient/Proxy Health economic outcomes *(CHU9D and EQ-5D-Y)*		X			X			X			X			X	X	
Caregiver sleep actigraphy[7]		X												X[8]		
Child sleep habits questionnaire & 1 week patient sleep diary		X												X[8]		

Schedule for follow up footnotes

[1] The eligibility criteria require trial specific activities (LRSQ score), therefore, confirmation of eligibility can only occur after informed consent.

[2] Administration of trial intervention must only occur once all baseline assessments have been completed. Administration should continue for full 52 weeks (Mon, Wed, Fri).

[3] Follow-up will be completed by phone / email.

[4] The 78-week follow up will only occur for patients when recruitment for the trial is still ongoing. Where this is not completed, a follow-up phone call at 28 days post treatment will be completed to assess safety events only.

[5] When hospitalised with acute LRTI. To occur whilst patient in follow up (either up to 52 week or 78 weeks)

[6] For Australian participants only (until UK contractual arrangements are in place

)[7] Optional consent for assessment and for UK participants only.

[8] Completed within the last 4 weeks of treatment. Collected during this visit. Reminded that completion required during follow up at 47 weeks.

7.3 Follow-up Assessments

7.3.1 Phone / Email Contact

The caregiver should be contacted by a delegated member of the research team, via their preferred method (phone / email), at 4, 8, 17, 21, 30, 34, 43 and 47 weeks after randomisation and the following information collected:

- Attendance at: Hospital and GP (including number of days unwell with LRTI where applicable)
- Changes in concomitant medication that could impact the respiratory systems (including, for example, anti-reflux medications)
- Changes to respiratory treatments / support
- Adverse events

When contacting the participant to collect the information, a maximum of three attempts should be made within ±1 week of the scheduled contact.

In addition, at the 47 week follow up the caregiver should be reminded that they will be commencing their last 4 weeks of study treatment and the following sleep assessments must be completed:

- Sleep actigraphy
- 1 week patient sleep diary

7.3.2 Face-to-Face Scheduled Visits

7.3.2.1 Face-to-Face Contact at 13 and 39 weeks after randomisation

Participants should return to their PARROT centre and a delegated member of the research team must complete the following follow-up assessments / collect the following from the patient / caregiver:

- Weight
- Completed IMP treatment diary
- Attendance at: hospital and GP (including number of days unwell with LRTI where applicable) - parent report for GP and chart review for hospital
- Changes to concomitant medications that could impact the respiratory systems (including, for example, anti-reflux medications)
- Changes to respiratory treatments / support (see section 7.4.2)
- Surgical and other interventions which may change respiratory function (see section 7.4.3)
- Adverse events.

The caregiver must complete the following follow-up assessments:

- LRSQ-Neuro questionnaire
- Resource use questionnaire
- Respiratory symptom questionnaire
- Warwick-Edinburgh Mental Wellbeing Scale.
- DISABKIDS (proxy completion)
- EQ-5D-Y (proxy completion)
- CHU9D (proxy completion).

If capacity allows the patient must also complete the following questionnaires:

- DISABKIDS
- EQ-5D-Y
- CHU9D.

Allowable window for visit: ±2 weeks.

7.3.2.2 Face-to-Face Contact at 26 weeks after randomisation

In addition to the follow-up assessments included in section 7.3.2.1 a delegated member of the research team must obtain a nasal swab (*for Australian participants only until UK contractual arrangements are in place*).

Allowable window for visit: ±2 weeks.

7.3.2.3 Face-to-Face Contact at 52 weeks after randomisation

In addition to the follow-up assessments included in section 7.3.2.1 and 7.3.2.2 the caregiver must complete the Child's Sleep Habits Questionnaire and any additional vaccinations since baseline recorded. The 1 week patient's sleep diary completed prior to the visit must also be collected.

This visit must only be scheduled for once the patient has completed their full 52 weeks of trial treatment. Therefore, the allowable window for this visit is +4 weeks.

7.3.2.4 Face-to Face Contact at 78 weeks after randomisation

These visits will only be completed when recruitment for PARROT is still ongoing.

All follow-up assessments listed in 7.3.2.1, 7.3.2.2 and 7.3.2.3 **excluding** the following:

- × Child's Sleep Habits Questionnaire
- × 1 week patient sleep diary
- × Sleep actigraphy
- × Completed IMP treatment diary

Allowable window for visit: ±2 weeks.

For participants that will not have a 78 week follow-up visit scheduled (as detailed above), a follow-up phone call at 28 days post-treatment will be completed to assess safety events only.

7.3.3 Face-to-Face Unscheduled Visits

If participants are admitted to their recruiting or designated centre with a new acute LRTI during their follow up period the participant should be managed in accordance with the site's local clinical practice. The following should also be taken:

1. Nasal swab (microbiology and resistance profiling)*
2. Nasal swab / nasopharyngeal aspirate (virology)*
3. Cough swab / sputum collection (bacteriology) *

LRTI assessment must also be completed against the definition of LRTI according to primary outcome.

Classification for a new acute LRTI: when it has been more than 2 weeks since the last admission due to acute LRTI.

**For Australian participants only (until UK contractual arrangements are in place).*

7.4 Special Assessments

7.4.1 LRSQ-Neuro Questionnaire

The LRSQ-Neuro questionnaire must be completed by the caregiver. It must be completed to confirm patient eligibility and then at follow-up visits: 13, 26, 39, 52 and 78 weeks (where applicable).

To calculate the LRSQ-Neuro score the following will be assessed:

Questionnaire Domain	Symptoms Assessed
Daytime Symptoms, Symptoms with Colds, Interval Symptoms (between colds)	Cough, wheeze, shortness of breath, 'rattly' chest
Night-time Symptoms	Cough, wheeze, shortness of breath, 'rattly' chest, snoring
Other Symptoms	Noisy breathing not from chest, noisy breathing from throat, fast breathing
Effects on child	Feeding, activity levels, sleep disturbance, fatigue
Effects on family	Family activities, adjustment to family life, disturbed sleep, worry / anxiety

The category scoring for each domain will be as follows:

Frequency	Score
Every	4
Most	3
Some	2
A few	1
Not at all	0

Example: If a participant has a cough **every** night then they would receive a score of **4** for night-time cough symptoms.

7.4.2 Changes to respiratory treatments / support

Changes to respiratory treatments and support includes the following and must be recorded accordingly:

- Chest Physiotherapy
- Cough Assist
- Oxygen
- Non-invasive ventilation
- Postural interventions

7.4.3 Surgical and other interventions which may change respiratory function

Surgical and other interventions that may change respiratory function includes the following and must be recorded accordingly:

- Botox injections
- Salivary duct ligation
- Spinal surgery
- Changes to feeding regime
- Changes to physical function
- Changes in home circumstances

7.4.4 Nasal Swabs / Nasopharyngeal Aspirate and Cough Swab / Sputum Collection*

Nasal swabs will be taken at baseline and during follow up visits at 26, 52 and 78 weeks (where applicable), as well as at any unscheduled visits after randomisation to:

- Assess microbiology
- Profile AMR

In addition, a nasal swab / nasopharyngeal aspirate and a cough swab / sputum collection should be taken each time a participant is in follow up and is hospitalised at the recruiting or designated centre for an unscheduled visit with acute LRTI (see section 7.3.3) in order to determine viral / bacterial causes.

Samples will be sent to the central laboratory for analysis in batches. The procedures for the processing and storage of sample until they are sent in batches to the central laboratory will be provided outside of this protocol.

Note: Nasal swabs / nasopharyngeal aspirate should be taken as specified, however, it is acknowledged that with this patient population, cough swabs / sputum collection may not always be possible and patient care must preside over these samples. The reasons for any missed swabs will be recorded.

**This section is only applicable for Australian participants (until UK contractual arrangements are in place).*

7.4.5 Patient Sleep Diary

The 1-week patient sleep diary will be given to the caregiver for completion at baseline and during the patient's final week of trial treatment. The diary should be returned via post to the recruiting centre or at the next face-to-face visit.

7.4.6 Sleep Actigraphy – For UK participants only

Sleep quantity and quality of primary caregivers will be assessed using actigraphy and the associated primary caregiver sleep log at baseline and during their final week of trial treatment for UK participants only.

Caregivers of children with neurodevelopmental disorders consistently report poor sleep quantity and quality, and this in turn is associated with other important outcomes including maternal depression(23).

Reliance on parent report increases the potential for reporter bias and actigraphy has the advantage of providing objective information on sleep habits in the person's natural sleep environment. We have therefore chosen to employ objective measures to demonstrate whether these impairments are related

to a perceived or a measurable deficit in sleep parameters. Actigraphy is a wrist-worn, accelerometer-based method of objective sleep assessment widely used in research and clinical practice and has been used successfully with adults.

Actigraphy data will let us look at baseline sleep patterns of primary caregivers and the impact of different treatments during the trial. Summary variables of sleep latency, total sleep time and sleep efficiency will be used for analysis.

LCTC will provide Activinsights with access to participant contact details via the PARROT contact database. Actigraphy equipment will be provided to primary caregiver directly by Activinsights along with instructions in the use of the equipment and its return. Contact details for troubleshooting any problems will also be provided by Activinsights. Activinsights will convert raw data into summary information for each participant according to published appropriate algorithmns(24). Analysis of the data will be completed by LCTC.

7.4.7 Hospital Episode Statistics – For UK participants only

HES will be requested from NHS Digital for the purposes of estimating hospital costs of patients treated in English hospitals (see section 2.4.2 Secondary Objectives and Outcome Measures). The patient / PPR / PLR will be fully and unambiguously informed as to the transfer of any personal data associated with obtaining and processing of HES data, and will consent to the disclosure of confidential information via an opt-in method. Consent for disclosure of confidential information relating to HES data (or its obtention) will not be a precondition of participants signing up to the trial.

The following data will be collected from NHS Digital: outpatient, inpatient (including critical care) and A&E attendances, from 3 months prior to randomisation and spanning the duration of each participant's involvement in the trial including any episodes that run over this period. Participant information (postcode, date of birth, NHS number, trial randomisation identifier and gender) will be collected by LCTC within a secure database, separate to the main trial database, which will enable LCTC to request HES data from NHS Digital. The database will only be accessible by authorised personnel working on the trial and shared with authorised personnel working at NHS Digital. At the time of the data request, the database will be sent securely to authorised personnel at NHS Digital and the HES data with the trial number will be securely transferred to health economists at the Centre for Health Economics and Medicines Evaluation (CHEME), Bangor University, who will be conducting the economic analysis. NHS Digital will be asked to remove participant personal identifiers such as NHS number, date of birth, pseudoHESID at source.

The only identifier present in the dataset will be the trial randomisation identifier and health economists at CHEME will not have any access to keys linking this to participant personal data. Access will be restricted only to health economists working on the trial via password protection. The HES data will be securely disposed in accordance with the CHEME and NHS Digital (Data Services for Commissioners) procedures.

7.5 Patient Transfer and Withdrawal

7.5.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient.

A copy of the patient Case Report Forms (CRFs) and consent form should be provided to the new centre. The LCTC should be notified via email of patient transfers.

If patient transfer to another participating centre is not possible then the patient would be considered as lost to follow-up (see section 7.6).

7.5.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

a. Patient / PPR / PLR withdraws consent (or assent).
b. Unacceptable safety events or intolerance.
c. Intercurrent illness preventing further treatment.
d. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a patient or their PPR / PLR wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the participant explicitly also withdraws consent for follow-up (see section 7.5.3).

If there is a temporary stop of trial treatment, for example, the participant is unable to collect their treatment within the designated window and run outs, then it should not be considered a withdrawal from the trial intervention and the participant should return to the administration of trial treatment when possible.

7.5.3 Withdrawal from Trial Completely

The patient, PPR or PLR are free to withdraw consent at any time without providing a reason. Participants who wish to withdraw consent for the trial will have pseudoanonymised data collected up to the point of that withdrawal of consent included in the analyses. If the caregiver decides they no longer wish to assist in the research, however another caregiver is happy to assist in their place, then this will be considered on a case-by-case basis.

Participants who withdraw from the trial completely will not contribute further data to the trial, unless this is required under applicable legislation (e.g. safety events) - the LCTC should be informed in writing and a withdrawal CRF should be completed.

The withdrawal CRF will also document if any samples that have been taken should be destroyed.

7.6 Loss to Follow-up

If a delegated researcher is repeatedly unable to contact a participant for follow-up, then attempts will be made through the participant's clinical care team and the participant's GP where possible. If contact via these methods are not successful, then the patient will be considered lost to follow up and recorded accordingly.

7.7 Notification of deaths

All deaths must be reported to the LCTC (within 7 days of becoming aware) using the withdrawal form. All deaths must also be reported to the LCTC and Chief Investigator within 24 hours using the SAE form.

7.8 Trial Closure

The end of the trial is defined to be the date on which data for all participants is locked and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Funder on the recommendation of the Trial Steering Committee (TSC) who are advised by the Independent Data and Safety Monitoring Committee (IDSMC).

Individual centres may be closed to recruitment prior to their intended recruitment end date if the TMG have concerns about their capacity or capability to deliver the trial, or for operational reasons whereby resources are better used at centres with better capacity to recruit.

8 TRIAL TREATMENT

8.1 Introduction

Patients will be randomised between azithromycin (active) and placebo (control). Blinded, trial specific supply of azithromycin and placebo will be provided to all participants.

8.2 Formulation, Packaging, Labelling, Storage and Stability

8.2.1 Azithromycin

Azithromycin will be supplied as powder for oral suspension. Each 5ml prepared suspension will contain 200mg azithromycin (refer to IMP Manual for a list of excipients).

The azithromycin powder for oral suspension will be packaged in plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. Refer to IMP Manual for additional guidance on storage, preparation and handling.

8.2.2 Placebo

Placebo matching azithromycin will be supplied as powder for oral suspension and supplied in a blinded manner. The placebo powder for oral suspension will be packaged in plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. Refer to IMP Manual for additional guidance on storage, preparation and handling.

8.3 Preparation, Dosage and Administration

Azithromycin or placebo will be orally administered 3 times weekly (single dose on Monday, Wednesday and Friday) for 52 weeks according to the dosing table below.

Weight	Dose to be taken on Mon, Wed, and Fri	Administration volume per dose
10 to 10.9 kg	100 mg	2.5 mL
11 to 12.9 kg	120 mg	3 mL
13 to 14.9 kg	140 mg	3.5 mL
15 to 16.9 kg	160 mg	4 mL
17 to 18.9 kg	180 mg	4.5 mL
19 to 21.9 kg	200 mg	5 mL
22 to 25.9 kg	240 mg	6 mL
26 to 30.9 kg	280 mg	7 mL
31 to 34.9 kg	320 mg	8 mL
35 to 38.9 kg	360 mg	9 mL
39 to 41.9 kg	400 mg	10 mL
42 to 44.9 kg	440 mg	11 mL
≥45 kg	500 mg	12.5 mL

Body weight will be collected at baseline, week 13, 26 and 39 visits (see section 7.3) and used for dosage calculation. If a participant experiences a ≥10% change in body weight (as compared to the weight recorded on previous visit), the dose of the trial intervention should be adjusted accordingly.

Detailed instructions including methods of reconstitution and administration will be provided to caregiver (refer to IMP Manual).

Treatment should commence within 3 weeks of randomisation and should continue for 52 weeks. Administration will not continue after the 52 week follow up visit, even if for example, there is a temporary halt in trial treatment.

8.3.1 Dose Modifications and management of Toxicity

In patients with mild to moderate renal impairment or mild to moderately impaired liver function, dose adjustment is not necessary.

In case of signs and symptoms of severe liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, trial medication should be stopped.

8.3.2 Specific restrictions

For trial subjects requiring oral or intravenous antibiotic treatment for acute infections, trial medication should be temporarily stopped and recommenced once the infection has been treated.

8.3.3 Overdose

An overdose is defined as a known deliberate or accidental administration of trial medication, to or by a trial subject, at a dose above that which is assigned to that individual subject according to the trial protocol. All cases of overdose (with or without associated Adverse Events (AEs) will be documented on the CRF. AEs associated with an overdose will be document on AE section of the CRF. SAEs associated with overdose should be reported according to the procedure outlined in section 9.9.2.

AEs experienced in higher than recommended doses of azithromycin were similar to those seen at normal doses (see section 9.2 for Reference Safety Information). In the event of overdosage, general symptomatic and supportive measures are indicated as required.

8.4 Unblinding

If the participant wishes to withdraw from the trial, and ceasing trial treatment is a viable option for their care, it should not be necessary for unblinding to occur.

Justification for unblinding: Unblinding is done on a per case basis (i.e., single participants) when knowing the treatment allocation is required to:

1. Enable treatment of safety event/s, or
2. Enable appropriate ongoing care upon cessation of allocated trial therapy.

However, due to centre set up for unblinding teams and due to the nature of trial treatment (active or placebo), until unblinding can occur all participants should be considered as on active treatment and trial treatment suspended where required.

In all instances of unblinding:

For UK participants:

1. The LCTC should be made aware before unblinding takes place. Where possible, permission to unblind an individual case should be requested via the trial coordinator at LCTC, who will then seek the agreement of the appropriate Chief Investigator or their agreed delegate.
2. To release treatment allocation of the specified participant, delegated members of the clinical trials pharmacy team will be unblinded and will have access to the treatment allocations for participants recruited at their centre.
3. Do not disclose treatment allocation to centre personnel unless knowledge is directly relevant to patient care.
4. Record and report in writing to the LCTC, by use of the unblinding CRF (including the identity of all recipients of the unblinding information), within 24 hours.
5. Do not disclose treatment allocation to LCTC personnel unless knowledge is required for pharmacovigilance purposes.

Please note, only in an emergency should unblinding occur without approval being in place from the CI and LCTC to enable management/treatment of patient.

For Australia participants:

1. Permission to unblind an individual case should be requested via the Australian CI (or agreed delegate) before unblinding takes place.
2. To release treatment allocation of the specified participant, delegated members of the clinical trials pharmacy team will be unblinded and will have access to the treatment allocations for participants recruited at their centre.
3. Do not disclose treatment allocation to centre personnel unless knowledge is directly relevant to patient care.
4. Record and report in writing to the LCTC, by use of the unblinding CRF (including the identity of all recipients of the unblinding information), within 24 hours.
5. Do not disclose treatment allocation to LCTC personnel unless knowledge is required for pharmacovigilance purposes.

Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) in both UK and Australia will be unblinded at the LCTC prior to reporting to the regulator.

8.4.1 Accidental unblinding

If accidental unblinding occurs, this must be reported to the LCTC and include details of:

1. Date of unblinding
2. Detailed explanation of circumstances
3. Recipients of unblinding information
4. Action to prevent further occurrence (if applicable)

If a participant becomes unblinded to their treatment allocation then they must complete their next, and final, scheduled face-to-face visit.

8.4.2 Unblinding at trial closure

Following trial closure, unblinding will occur and each site will be informed of the treatment allocation per recruited patient at their site.

8.5 Accountability Procedures for Trial Treatments

The investigator or designee must ensure that the trial medication is used in accordance with the protocol and is dispensed only to subjects enrolled in the trial. To document appropriate accountability of trial medication, the investigator or designee must maintain records of all trial medication delivery to the site, site inventory, dispensation, and disposal following sponsor approval.

Upon receipt of trial medication, contents of the shipments must be verified against the packing list, and the trial medication is in good condition. If there are discrepancies, the LCTC should be informed immediately. Record of inventory of all trial medication must be recorded on a sponsor-approved drug accountability log.

8.6 Assessment of Compliance with Trial Treatments

To assess compliance with trial treatment, the caregiver must complete the IMP treatment diary. The completed diary should be returned at the 13, 26, 39 and 52 week follow up visits.

8.7 Concomitant Medications / Treatments

8.7.1 Medications: Permitted

Other than those listed under exclusion criteria, all necessary concomitant medications are allowed in this trial as clinically indicated and at the clinician's discretion.

8.7.2 Medications: Precautions Required

The following list is not exhaustive, but particular caution should be applied to PARROT patients in the following circumstances:

- Co-administration with antacids (the trial drug should not be taken simultaneously with antacids)
- Co-administration with active substance known to prolong QT interval
- Co-administration with digoxin: monitor digoxin concentration
- Co-administration with ticagrelor
- Co-administration with aminophylline / theophylline.

It is clinical decision if, for example, the trial drug should be stopped temporarily whilst any of the above medication is administered to the patient.

In addition, the trial drug should be stopped temporarily if the patient is receiving another course of systemic antibiotics.

8.7.3 Data on Concomitant Medication

Concomitant medication that could impact the respiratory systems (including, for example, anti-reflux medications) and interventions that may change respiratory systems, including 'stepping down' asthma treatments, chest physiotherapy and cough-assist will be collected (see sections 7.4.2 and 7.4.3), unless needed for clinical assessments e.g. when assessing serious adverse events (SAEs) and a drug interaction is considered possible.

9 SAFETY REPORTING

9.1 Time Period for Safety Reporting

Safety reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs) will be completed from first administration of trial treatment until 28 days following completion of trial treatment.

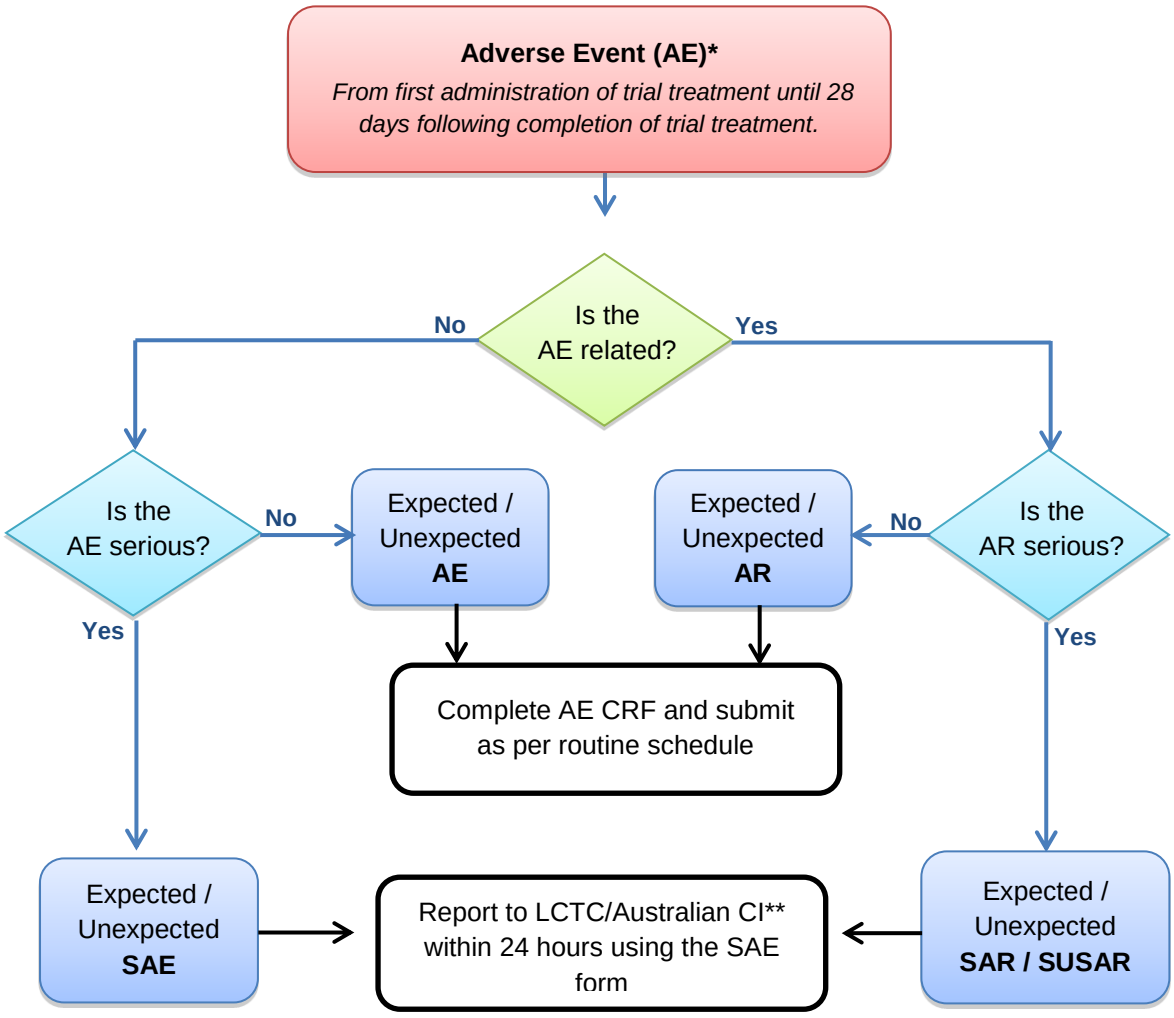
After this time period, sites should notify the appropriate coordinating centre of SARs only.

9.2 Reference Safety Information

The Reference Safety Information (RSI) in PARROT and used to assess expectedness (see section 9.7) is section 4.8 of the Azithromycin 200 mg in 5 ml suspension Summary of Product Characteristics (SmPC). MA number: PL 04416/0782.

As the placebo is inert there are no expected adverse reactions, therefore any serious adverse reactions thought to be related to the placebo would be unexpected and reported as a potential SUSAR.

9.3 Flowchart for Reporting Requirements of Safety Events



** If an adverse event occurs in the 28 days following last treatment administration, the above process should still be followed. After this time period, SARs should be notified as outlined in the above process.*

*** For UK participants, the coordinating centre is LCTC. For Australian participants, the report should be provided to both LCTC and the Australian CI (or agreed delegate).*

9.4 Terms and Definitions

Table 1: Terms and Definitions of Events

Adverse Event (AE)	"Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment."
Adverse *Reaction* (AR)	"All untoward and unintended responses to an investigational medicinal product related to any dose administered". ARs also include "medication errors and uses outside of the protocol (including misuse and abuse)".
***Serious* Adverse Event (SAE)**	An event is termed "serious" if it: • results in death; • is life-threatening: • requires hospitalisation, or prolongs existing hospitalisation • results in persistent or significant disability or incapacity: • consists of a congenital anomaly or birth defect: • an otherwise medically significant event which jeopardises the subject, or requires intervention to prevent any of the above.
Serious Adverse *Reaction* (SAR)	An event assessed as "related" and "serious".
***Suspected Unexpected* Serious Adverse Reaction (SUSAR)**	An event assessed as "related", "unexpected" and "serious".

9.5 Severity / Grading of Adverse Events

The assignment of the severity / grading should be made by the investigator responsible for the care of the participant using the definitions in Table 2: Definitions of Severity / Grading.

Table 2: Definitions of Severity / Grading

Mild	Does not interfere with routine activities
Moderate	Interferes with routine activities
Severe	Impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a SAE.

9.6 Relationship to Trial Treatment

The assignment of the causality, for both azithromycin and placebo, should be made by the investigator responsible for the care of the participant using the definitions in Table 3: Definitions of Causality.

If any doubt about the causality exists, the investigator should inform the LCTC who will notify the CI. In the case of discrepant views on causality between the investigator and others, the CA(s) will be informed of both points of view.

Table 3: Definitions of Causality

Unrelated	There is no evidence of any causal relationship. *N.B. An alternative cause for the AE should be given.*
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. 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 (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

9.7 Expectedness

An AE whose causal relationship to the trial treatment is assessed by the investigator as "possibly", "probably", or "almost certainly" is an AR.

For all ARs graded as serious, the CI (or delegate) will also assess for expectedness. If **unexpected** (see section 9.2 for RSI) the SAR will be reported as a SUSAR.

9.8 Follow-up after Adverse Events

All AEs should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes in accordance with the SAE CRF.

9.9 Reporting Procedures

PIs and delegated Investigators are responsible for reporting all AEs that are observed or reported during the trial and any SAEs that they become aware of after that. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning AE reporting should be directed to the LCTC (UK) or designated Australian medical expert in the first instance. Section 9.2 includes a flowchart to aid determining the reporting requirements.

9.9.1 Non serious AEs

All such events, whether expected or not, should be recorded on an AE Form, which should be transmitted to the LCTC within seven days of the site becoming aware of the event.

9.9.2 SAEs / SUSARs

9.9.2.1 Investigator Responsibilities

SAEs and SUSARs should be reported to the LCTC (*UK & Australia*) and the Australian CI/agreed delegate (*Australia only*) on an SAE form by the site **within 24 hours** of the centre becoming aware of the event. In Australia, PIs are also required to report any SSIs or SUSARs to their institution within **72 hours** of becoming aware of the event.

The SAE form should be completed by a delegated investigator and asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality (relationship to IMP and placebo). In the absence of a delegated investigator, the form should be completed and signed by an alternative member of the research centre trial team and submitted to the LCTC (*UK & Australia*) and the Australian CI/agreed delegate (*Australia only*). As soon as possible thereafter the delegated investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC (*UK & Australia*) and Australian CI/agreed delegate (*Australia only*).

The minimum information required for reporting is as follows:

- Valid EudraCT number
- Sponsor trial number
- One identifiable coded subject
- One identifiable reporter
- One SAE
- One suspect IMP (including active substance name)
- A causality assessment.

When submitting an SAE to the LCTC (*UK & Australia*) and the Australian CI/agreed delegate (*Australia only)*, centres should also telephone the appropriate (*UK or Australia*) Trial Co-ordinator / Data Manager where possible to advise that a SAE report has been submitted. SAE forms should be sent via a secure method, such as encrypted emails to: parrot@liverpool.ac.uk.

If the event has not resolved at the time of reporting, additional information should be noted on an SAE form and submitted to the LCTC (*UK & Australia*) and Australian CI (*Australia*) within 5 days of the information becoming available. The participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Extra, annotated information and / or copies of test results may be provided separately.

The responsible investigator must also **notify** their R&D department of the event if appropriate (as per standard local governance procedures).

9.9.2.2 LCTC (UK) or Menzies School of Health Research (Australia) Responsibilities

For the UK, Sponsor has delegated LCTC to report SUSARs and other SAEs to the applicable CAs and ECs as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the LCTC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the LCTC first becoming aware of the reaction.
- A list of all SAEs (expected and unexpected) must be reported annually.

For Australia, Menzies School of Health Research as Sponsor will report SUSARs, SSIs and other SAEs to the applicable CAs and ECs as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the Menzies School of Health Research is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the Menzies School of Health Research first becoming aware of the reaction.
- A list of all SAEs (expected and unexpected) must be reported annually.
- All significant safety issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial and all other significant safety issues should be notified within 15 calendar days of the sponsor being made aware of the issue.

Staff at the LCTC (*UK*) will liaise with the UK CI (or designated other specified in the protocol) who will review the seriousness and expectedness for all UK SAEs received. The Australian CI (or designated other specified in the protocol) will review the seriousness and expectedness for all SAEs received from Australian sites. Investigator reports of SAEs will be reviewed immediately and those that are identified as SUSARs will be reported to the applicable CAs and ECs. The causality assessment given by the Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

All PIs will be informed of any SUSARs that occur throughout the trial.

The reporting Sponsor (or delegate) will notify the co-Sponsor of any reported SUSARs in line with the timelines outlined above for the purpose of any additional reporting that may be required along with evidence of submissions to ECs and/or CAs, acknowledgments and any further communications as they become available.

9.9.3 Reporting of Pregnancy

Due to the patient population, pregnancies are unlikely. However, all pregnancies should be reported on a “Pregnancy CRF”, returned to the LCTC within 24 hours of awareness and the pregnancy followed up until after the outcome. Participants will also be informed to discontinue trial treatment.

9.9.4 Maintenance of Blinding

Systems for SUSAR and SAE reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial treatments unless criteria have been fulfilled (section 7.7) and unblinding has taken place.

Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the LCTC. Following unblinding, any confirmed SUSARs would be reported to the regulator.

9.9.5 Safety reports

Safety reports will be generated during the course of the trial that allows for monitoring of SAE and AE reporting rates across centres. The UK Sponsor (or delegate) and Australian Sponsor will send the applicable regulatory reports containing a list of all SAEs to the applicable CAs and ECs.

Any concerns raised by the IDSMC or inconsistencies noted at a given centre may prompt additional training at centres, with the potential for the LCTC (or Australian delegate) to carry out centre visits if there is suspicion of unreported ARs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

9.9.6 Urgent Safety Measures

An urgent safety measure (USM) is a procedure not defined by the protocol, which is put in place prior to authorisation by the CAs and ECs in order to protect clinical trial participants from any immediate hazard to their health and safety.

The Sponsor (or delegate) will notify the applicable CA and ECs immediately and, in any event, within the following timelines that such a measure has been taken, the reasons why it has been taken and the plan for further action:

<table>
<tr><th>USM</th><th>UK</th><th>Australia</th></tr>
<tr><td>Taken by the trial</td><td rowspan="2">Telephone (ideally within 24 hours) and a notice in writing sent within 3 days.</td><td>Email within 24 hours (where possible) and in any case, no later than 72 hours of the measure being taken.</td></tr>
<tr><td>Taken by another country's regulatory agency</td><td>Email without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action.</td></tr>
</table>

After discussion with the CAs and ECs, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

If the trial is temporarily halted, it may not recommence until authorised to do so by the CAs and ECs. If the trial is permanently terminated before the date specified for its conclusion, as detailed in section 7.8, the Sponsor should notify the CA and EC within 15 days of the date of termination.

9.10 Contact Details and Out-of-hours Medical Cover

The safety profile for azithromycin suggests that adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures should be completed as required. Consequently, there will be no out-of-hours medical cover. However, individual contact details stated at the beginning of this protocol can be used for clinical queries as stated / required.

10 STATISTICAL CONSIDERATIONS

10.1 Introduction

Separate Statistical Analysis Plans (SAPs) will be developed prior to the final analyses of the trial. The main features of these planned statistical analyses are included here in the protocol.

10.2 Method of Randomisation

Participants will be equally randomised to all treatment arms currently in the trial using a secure (24-hour) web-based randomisation programme controlled centrally by LCTC to ensure allocation concealment. Randomisation lists will be generated using block randomisation with random variable block length, stratified by site. The randomisation list will be generated by an independent statistician at the LCTC who is not otherwise involved in the PARROT trial.

10.3 Sample Size calculation

To detect a 30% reduction in hospitalisation rate in children with NI and respiratory symptoms at risk of LRTI, with 90% power (alpha 0.05), we would require 225 patients per group, increasing to 250 allowing for 10% loss to follow-up/attrition, i.e. 500 children in total.

Sample size calculations have focussed on patients who fulfil the two main inclusion criteria of >2 courses of antibiotics and/or one hospitalisation with LRTI over the previous year, and who have persistent respiratory symptoms (assessed using a modified respiratory symptom score (LRSQ-Neuro).

Based on our pilot data from a cohort of 158 children with NI from North-West England, 54 children received ≥2 courses of antibiotics for respiratory illnesses over the previous year of which 43 had a LRSQ-Neuro score ≥ 95% CI for their age. Of these, 21/43 (49%) were hospitalised over the previous year. A 30% treatment effect decreases hospitalisation from 49% to 34%. To detect a relative decrease of 30% between the two groups would require a total of 250 participants in each group (allowing for a 10% loss to follow up) with a 90% power and a Type I error rate of 5%.

Calculations of effect size have been based on a previous RCT of LRTI reduction using azithromycin in children with bronchiectasis(13), and on discussions with parents and healthcare professionals.

10.3.1 Feasibility (attaining recruitment targets)

We surveyed willingness to participate in a trial of prophylactic antibiotics to prevent respiratory symptoms. Of 37 children hospitalised within the last year with a respiratory exacerbation, 15 (43%) expressed an interest in participation, whilst of 54 children prescribed ≥2 courses of antibiotics, 20 (37%) expressed an interest.

As part of feasibility work for this trial, we have personally contacted leads for specialist neuro-respiratory clinics in 10 large UK tertiary centres, all of whom have agreed to take part in this trial. In July-August 2016, we also circulated a Site Expression of Interest (EoI) form through the NIHR Clinical Research Network to UK paediatric secondary/tertiary centres. Despite the summer holidays, we had 18 positive replies from centres around the UK. The site EoI form asked specifically about numbers of children fulfilling our eligibility criteria. In total, it was estimated that there were 316 children in these sites fulfilling our eligibility criteria and who were treatment naïve, and another 133 children who were already taking antibiotic prophylaxis. Based on these responses, we have calculated recruitment rates/site

(15 patients/site for tertiary centres and 5 patients/site in smaller centres in the UK) and recruitment duration (3 years).

10.4 Interim Monitoring and Analyses

There are no planned interim analyses for this trial.

Analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an IDSMC. These analyses will be performed at the LCTC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

10.5 Analysis Plan

A Statistical Analysis Plan (SAP) will be developed for use in the analyses of the trial.

10.5.1 Clinical effectiveness evaluation

The intention to treat principle will be used and data presented in accordance to CONSORT. In brief, all tests conducted will be 2-sided at 5% significance. For the primary outcome, the number of participants (and percentages) who are hospitalised will be presented for each treatment arm. The relative risk together with 95% confidence interval will be reported along with a two-sided p-value from a chi-square test. For secondary outcomes, binary outcomes will be analysed using a two-group chi-square test and presented as relative risks with 95% confidence interval. Continuous outcomes that are measured at baseline and then at subsequent treatment visits will be analysed using a repeated measures random effects model. Count data (e.g. number of rescue antibiotics courses) will be presented as the mean number of events per unit of time for each treatment group and will be comparted by analysing the incidence rates. The incident rate ratio and associated 95%CI will be presented. Time to event data will be presented using Kaplan Meier plots and will use the log rank test to determine statistical significance.

Missing data will be routinely and frequently monitored with strategies developed to minimise its occurrence. The primary analysis will not use methods of imputation for missing data but will report on known reasons for loss to follow up and information captured prior to that point.

10.5.2 Health economic evaluation

A detailed Health Economics Analysis Plan (HEAP) will be developed prior to unblinding. The health economic analysis will adopt the perspective reflecting the NHS and Personal Social Services in the UK. Resource use will be collected and analysed for all patients. Costs will include those of azithromycin, duration of hospital admission including paediatric intensive care, other antibiotic treatment and concomitant medications, contact with health professionals in primary care and social services. Resource use will be based on questionnaire and HES obtained from NHS Digital. Unit cost data will be obtained from routine hospital data (NHS reference costs) and other resources such as the British National Formulary and Curtis' unit costs of health and social care.

The primary economic outcome will be the incremental cost per QALY gained, estimated by administering the CHU9D. The CHU9D is a generic, preference-based utility measure that has been developed exclusively with and for children. It has preference weights available for the UK (standard

gamble) and for Australia (using profile case best worst scaling methods). The number of QALYs experienced by each patient will be calculated as the area under the curve, using the trapezoidal rule, and corrected for baseline utility score. A secondary analysis will use the EuroQol EQ-5D-Y (youth version) for estimation of utility scores. Proxy completion (by caregiver) of the CHU9D and EQ-5D-Y questionnaires will be requested for all patients as it is expected that most patients will be unable to complete themselves. However, those patients who can complete the CHU9D and EQ-5D-Y questionnaires will also do so.

Costs and benefits occurring after the first year will be discounted at 3.5% per annum. Total costs and QALYs will be used to calculate the incremental cost- effectiveness ratio (ICER) of prophylactic azithromycin. Where appropriate, missing resource use or health outcome data will be imputed. Non-parametric bootstrapped 95% confidence intervals for items of resource use, costs and QALYs will be estimated (10,000 replicates).

We will also employ simple parametric approaches for analysing cost and QALY data that assume normal distributions given the large samples where the near-normality of sample means is approximated. Should the data indicate otherwise, we will develop a generalized linear model, to deal with problems such as skewness. Stratified cost-effectiveness analyses will be conducted on important, pre-specified patient subgroups. Estimates of ICERs will be compared with the NICE £20,000 to £30,000 per QALY threshold of cost-effectiveness, and a range of one-way sensitivity analyses will be conducted to assess the robustness of the analysis. Multivariate sensitivity analyses will be applied where interaction effects are suspected, and the joint uncertainty in costs and benefits will be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.

11 REGULATORY AND ETHICAL APPROVALS

11.1 Statement of Compliance

The trial will be carried out in accordance with the applicable regulations in the UK and Australia.

11.2 Regulatory Approval

This trial involves IMPs, therefore, will be approved by the applicable CAs prior to trial recruitment in each recruiting country. For the UK, the CA approval will be obtained from the MHRA. For Australia, this will be obtained from the Therapeutic Good Administration (TGA).

11.3 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The specific ethical considerations are:

A. Recruitment of children and adults lacking capacity

Due to the patient population for this trial, potentially eligible patients may not have capacity to consent or assent (as applicable) for themselves. Therefore, for these patients their PPR / PLR will be asked to provide consent on behalf of the patient. The informed consent given by the PPR / PLR shall represent the presumed will of the patient. However, if it is appropriate and based on the patient's capacity, patients will receive an information leaflet about the trial for themselves.

B. Inclusion criteria includes a 'washout' period

To be eligible for the trial, patients must be either azithromycin naïve or must have a 13-week 'washout' period prior to enrolment, as outlined in the inclusion criteria. It is possible that during the 'washout' period patients could become more symptomatic or that a respiratory exacerbation could be precipitated. The potential for this to happen will be minimised as every effort will be made to undertake the washout over the summer months. In addition, before the washout period can take place, the paediatrician managing the patient's respiratory symptoms should be consulted to determine if there are any safety concerns at the point of considering enrolment which would prevent the patient from stopping prophylactic antibiotics. Families will be advised of this inclusion criterion and the potential risks prior to providing informed consent.

11.4 Ethical and Local Governance Approval

Ethical and governance approval will be obtained prior to trial recruitment in each recruiting country.

For UK centres, favourable ethical opinion will be obtained from a central Research Ethics Committee (REC). Prior to opening a centre to recruitment, LCTC will ensure that local approvals are obtained.

For Australian centres, each centre will obtain an institutional-level approval by their Human Research Ethics Committee (HREC) prior to opening to recruitment.

11.5 Protocol Deviation and Serious Breaches

A breach of the protocol or GCP is 'serious' if it meets the regulatory definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial".

If any persons involved in the conduct of the trial become aware of a potential serious/suspected breach, they must report this as follows:-

- UK: Report potential serious breach immediately to the LCTC who will in turn notify UK Sponsor on the same day they become aware of the potential serious breach.
- Australia: Report suspected breach to Australian Sponsor within 72 hours of identifying the suspected breach.

The applicable Sponsor will assess the breach and determine if it meets the criteria of a 'serious' /'suspected'breach of GCP or protocol and therefore requires expedited reporting to the applicable CA and ECs.

In determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants, the Sponsor may seek advice from medical expert members of the TMG and / or of the independent oversight committees (IDSMC and TSC); Australian Sponsor may also consult with the reviewing HREC. In determining whether or not the breach is likely to significantly affect the scientific value of the trial, the Sponsor may seek advice form the Trial Statistician. However, the applicable Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to the applicable CA and ECs.

Breaches confirmed as 'serious' will be reported as follows:

- UK: Sponsor (or delegate) will report the confirmed serious breach to REC and MHRA within 7 days of becoming aware of the potential serious breach.
- Australia: Sponsor will report the confirmed serious breach to the reviewing HREC within 7 days of confirming a serious breach has occurred. If the serious breach occurred at a trial site, Sponsor will also notify the trial site's principal investigator (PI) within 7 days of confirming a serious breach has occurred; the PI must subsequently report this to their institution (research governance office) within 72 hours of being notified of the serious breach. Only confirmed serious breaches which involve ''a defective product that may have wider implications for the supply chain for that marketed product" will be reported to TGA.

All confirmed serious breaches (UK and Australia) will be notified to the TMG, IDSMC and TSC at their next meeting. Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, EC or CA, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

The reporting Sponsor (or delegate) will provide a copy of any completed serious breach reports to the co-Sponsor within the above reporting timelines for their records and for the purpose of any additional reporting that may be required. Evidence of submissions to ECs and/or CAs, acknowledgments and any further communications will also be provided to the co-Sponsor as they become available.

Incidence of protocol non-compliance are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

11.6 Trial Discontinuation

In the event that the trial is discontinued, participants will return to their local standard care.

12 DATA MANAGEMENT AND TRIAL MONITORING

Details of the monitoring to be carried out are included in the PARROT Trial Monitoring Plan. Trial Oversight Committees related to the monitoring of the trial are detailed in section 14.4.

12.1 Source Documents

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF.

The CRF will be considered the source document for data where no prior record exists and which is recorded directly in the CRF. A PARROT source document checklist will be produced for each centre.

The date(s) when the informed consent process was completed, including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

12.2 Data Capture Methods

A paper CRF is the primary data collection instrument for the trial. All data requested on the CRF must be recorded. All missing data must be explained. All entries should and corrections made to GCP standards.

Questionnaires are also used as data collection tools for PARROT and are source documents. Centres should photocopy them in order to retain a copy at centre before mailing originals to LCTC.

12.3 Monitoring

12.3.1 Central Monitoring

Data stored at LCTC will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the centre in the form of data queries. Data query forms will be produced at the LCTC from the trial database and sent either electronically or through the post to a named individual (as listed on the centre delegation log).

Centres will respond to the queries providing an explanation / resolution to the discrepancies and return the data query forms to LCTC. The forms will then be filed along with the appropriate CRF and the appropriate corrections made on the database. There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

Centres will also submit monthly logs documenting the number of patients screened, eligible and randomised.

If centres do not remain engaged with the trial then they may be closed to recruitment and additional centres identified.

12.3.2 Clinical Centre Monitoring

In order to perform their role effectively, the TC (or monitor), Data Manager and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the PISC.

12.4 Confidentiality

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

CRFs will be labelled with the patient's initials and unique trial screening and / or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

To enable verification that appropriate informed consent is obtained, copies of participant's signed informed consent forms will be supplied to the LCTC (*UK*) or Menzies School of Health Research (*Australia*) by recruiting centres. Therefore, name data will be transferred to the LCTC (*UK sites only*)/ Menzies School of Health Research (*Australian sites only*). This transfer of identifiable data is disclosed in the PISC. The University of Liverpool, Bangor University and Menzies School of Health Research are all data controllers for the trial and will preserve the confidentiality of participants taking part in the trial. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Centres should ensure that other trial documents are not posted in the same envelope as the consent form as there is a risk to patient confidentiality.

Activinsights will be responsible for providing the wrist watches for sleep actigraphy to UK caregivers and converting raw data into summary data for each participant for analysis by LCTC. Therefore, they will be required to receive contact details including name, address and telephone details.

12.5 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

12.6 Records Retention

The PI at each centre must make arrangements to store trial documents including:

- Investigator Site File*
- Pharmacy Site File*
- All relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from CAs).

**Must include essential documents as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice).*

Trial documents must be stored for the full archiving period as defined in contracts (25 years) and in compliance with the principles of GCP. Electronic HES Data will be stored and destroyed safely, in accordance with the Data Protection Laws and in line with our agreement with NHS Digital governing secure data deletion methods.

PIs will destroy documents at the end of this period upon instruction by the Sponsor / LCTC.
The PI is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the trust or retires before the end of required storage period. Delegation must be documented in writing.

13 INDEMNITY

13.1 UK

In the UK, PARROT is sponsored by the University of Liverpool and co-ordinated by the LCTC. The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of clinical research, including but not limited to the authorship of the Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

As this is an investigator-initiated trial, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

13.2 Australia

In Australia, PARROT is sponsored by the Menzies School of Health Research.

For the Australian sites, indemnity for trial related purposes will be covered under the Menzies School of Health Research Clinical Trials Insurance.

14 ROLES AND RESPONSIBILITIES

14.1 Role of Trial Sponsor and Trial Funder

The UK trial Sponsor is the University of Liverpool. The Australian trial Sponsor is the Menzies School of Health Research.

The Sponsor for each member state will ensure that clear agreements are reached, documented and carried out, respecting the dignity, rights, safety and wellbeing of participants and the relationship with healthcare professionals. This will provide for proper design, management, initiation, conduct, monitoring, data collection, data analysis, data protection, financing and reporting of this trial meeting appropriate scientific, legal and regulatory standards. The responsibility for design, conduct, management, data analysis, data interpretation, manuscript writing, and dissemination of results is delegated to the TMG.

The funders of this trial are the National Institute of Health Research Technology Assessment Programme (for the UK) and the National Health and Medical Research Council (for Australia).

The funders will assure the quality of the trial, taking the lead in establishing that the research proposal is worthwhile, of high scientific quality, has an appropriate research infrastructure with expert clinical trial management, has the capacity to comply with the principles of GCP and proper use of the funds representing good value for money.

14.2 Funding and Support in Kind

Funder(s)	Financial and Non-financial Support Given
National Institute of Health Research Technology Assessment Programme	Financial funding for UK aspects of the trial
National Health and Medical Research Council	Financial funding for Australian aspects of the trial

14.3 Protocol Contributors

Name	Affiliations	Contribution to protocol
Paul McNamara	Alder Hey Children's Foundation NHS Trust and University of Liverpool (UK)	Inception of trial (UK), led the writing of this protocol, clinical and scientific arrangements, trial design and conduct
Anne Chang	Menzies School of Health Research (Australia)	Inception of trial (Australia), led the writing of this protocol, clinical and scientific arrangements, trial design and conduct
Dannii Clayton	LCTC, University of Liverpool (UK)	Statistical arrangements, trial design and conduct
Jonathan Grigg	Queen Mary University of London (UK)	Clinical arrangements, trial design and conduct
Paul Gringras	Guy's & St Thomas' NHS Foundation Trust (UK)	Clinical arrangements, trial design and conduct (with focus on sleep research)
Michelle Heys	University College London (UK)	Clinical arrangements, trial design and conduct

Name	Affiliations	Contribution to protocol
Helen Hickey	LCTC, University of Liverpool (UK)	Protocol development, governance arrangements and trial conduct
Dyfrig Hughes	Bangor University (UK)	Led health economic arrangements
Amy Humphreys	LCTC, University of Liverpool (UK)	Protocol development, governance arrangements and trial conduct
Ashley Jones	LCTC, University of Liverpool (UK)	Led statistical arrangements, trial design and conduct
Christopher Morris	University of Exeter (UK)	Trial design and conduct
Jeremy Parr	Newcastle University (UK)	Clinical arrangements, trial design and conduct
Matthew Peak	Alder Hey Children's Foundation NHS Trust (UK)	Trial design and conduct
Dinah Reddihough	The Royal Children's Hospital, Parkville (Australia)	Clinical arrangements, trial design and conduct
Calum Semple	Alder Hey Children's Foundation NHS Trust and University of Liverpool (UK)	Clinical arrangements, trial design and conduct
Hayley Smallman	PPI Representative, University of Liverpool (UK)	Trial design and conduct
Leanne Turner	Alder Hey Children's Foundation NHS Trust (UK)	Clinical arrangements, trial design and conduct
Mandy Wan	Guy's & St Thomas' NHS Foundation Trust (UK)	IMP arrangements, trial design and conduct
Craig Winstanley	University of Liverpool (UK)	Trial design and conduct (Microbiology)
Katrina Williams	Monash University (Australia)	Clinical arrangements, trial design and conduct
Paula Williamson	LCTC, University of Liverpool (UK)	Statistical arrangements, trial design and conduct

14.4 Trial Committees

14.4.1 Trial Management Group (TMG)

A TMG will be formed comprising the CI, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG will be responsible for the day-to-day running and management of the trial and will meet regularly.

14.4.2 Trial Steering Committee (TSC)

The TSC will include an independent chairperson, an independent expert and an independent biostatistician. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

14.4.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC will include an independent chairperson, an independent expert and an independent biostatistician. The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and then will meet at least annually. Details of the interim analysis and monitoring are provided in section 9. The IDSMC will provide a recommendation to the TSC concerning the continuation of the trial.

15 PUBLICATION AND DISSEMINATION

15.1 Publication Policy

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected.

All publications shall include a list of participants, and if there are named authors, these should include the trial's CIs, Statistician(s), Health Economist(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the acknowledgements / appendix of the main publication.

15.2 Dissemination to Key Stakeholders

Results of this trial disseminated as early as possible to appropriately inform policy and practice. This will initially be achieved by academic dissemination of the results at international conferences, including the Royal College of Paediatrics and Child Health (RCPCH) annual meeting, as well as the American Thoracic Society and European Respiratory Society meetings, and through high impact publications including the HTA open access journal. It is expected that this research will contribute to an update of the Cochrane review. We will also make the trial data freely available in an open access database.

Families, clinicians, commissioners and managers will all need to know the results of this trial and we will use diverse forms of providing information to reach each stakeholder group. We will present our findings at family events and charity conferences, via plain language summaries using social media, and through charity newsletters, the PARROT website and other relevant websites such as 'Together for Short Lives' and 'Cerebra' in the UK, and the equivalent organisations in Australia (such as the Cerebral Palsy Alliance, the Cerebral Palsy Support Network).

We will then work to include the results into national and international guidelines through discussions with colleagues in the key stakeholder organisations such as the RCPCH, British Association for Community Child Health (BACCH), the British Academy of Childhood Disability (BACD) and the British Paediatric Respiratory Society (BPRS), and their equivalent in Australia.

15.3 Data Sharing

Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG. Publications shall include a list of participating PIs and collaborators.

16 CHRONOLOGY OF PROTOCOL AMENDMENTS

16.1 Version 1.0 (12/07/2019)

Summary of Amendments		
Section Number	**Section Title**	**Summary of Changes**
N/A	N/A	N/A – Original approved version.

16.2 Version 2.0 (16/12/2019)

Summary of Amendments		
Section Number	**Section Title**	**Summary of Changes**
N/A	Front page	• Resized PARROT logo to make bigger. • Addition of LCTC logo.
N/A	Contact details	• Change to laboratory contact details. • UK individuals; clarification added that UK medical experts will evaluate UK SAE reports. • Australian individuals; clarification added that Australian medical experts will evaluate Australian SAE reports.
N/A	Glossary	• Updated to add in missing terms.
1.0	Protocol summary	• Addition of reference to nebulised antibiotics. • Addition of secondary objective; *To assess residual impact of 52 weeks antibiotic prophylaxis at 78 weeks.*
5.1	Inclusion criteria	• Addition of reference to nebulised antibiotics.
6.4	Baseline assessments	• Addition of confirmation that nasal swabs will only initially be taken for Australian participants.
6.5.3	Contact database failure	• Inclusion of instructions for the failure of the contact database.
7.2	Schedule for follow-up	• Addition of confirmation that nasal swabs will only initially be taken for Australian participants. • Addition of follow-up phone call at 28 days post-treatment to assess safety events, for participants not completing the 78 week follow-up visit.
7.3.2	Face-to-face scheduled visits	• Addition of confirmation that nasal swabs will only initially be taken for Australian participants. • Addition of reference to completed IMP diary at follow-up. • Addition of follow-up phone call at 28 days post-treatment to assess safety events, for

		participants not completing the 78 week follow-up visit.
7.4.4	Nasal swabs/ Nasopharyngeal Aspirate and Cough Swab / Sputum Collection	• Addition of confirmation that nasal swabs will only initially be taken for Australian participants.
7.7	Notification of deaths	• Addition of section outlining process for notification of deaths.
9.1	Time Period for Safety Reporting	• Addition of 28 day safety monitoring period following completion of trial treatment.
9.2	Reference Safety Information	• Addition of statement regarding placebo and expected safety events.
9.3	Flowchart for Reporting Requirements of Safety Events	• Addition of 28 day safety monitoring period following completion of trial treatment.
10.3	Sample size calculation	• Removal of paragraph containing information discussed in the subsequent paragraph.
10.5	Analysis plan	• Removal of reference to interim analysis.
11.3	Ethical Considerations	• Inclusion of reference to inclusion criteria.
N/A	N/A	• Clarifications to processes and typographical error corrections made throughout.

16.3 Version 3.0 (12/03/2020)

Summary of Amendments		
Section Number	**Section Title**	**Summary of Changes**
N/A	Front page	• Added CTA reference number • Added REC reference number
1.0	Protocol summary	• Clarification that before the washout period can take place, the paediatrician managing the patient's respiratory symptoms should be consulted to determine if there are any safety concerns at the point of considering enrolment which would prevent the patient from stopping prophylactic antibiotics.
5.1	Inclusion criteria	• Clarification that before the washout period can take place, the paediatrician managing the patient's respiratory symptoms should be consulted to determine if there are any safety concerns at the point of considering enrolment which would prevent the patient from stopping prophylactic antibiotics.
6.2	Informed consent	• Updated to include details of assent for 6-15 year olds.

11.3	Ethical Considerations	• Clarification that before the washout period can take place, the paediatrician managing the patient's respiratory symptoms should be consulted to determine if there are any safety concerns at the point of considering enrolment which would prevent the patient from stopping prophylactic antibiotics.

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18 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and / or EC review are submitted as separate version controlled documents.