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Prophylactic antibiotics to prevent chest infections in children with neurological impairment

Submission date
03/02/2020

Recruitment status
No longer recruiting

Registration date
22/04/2020

Overall study status
Completed

Last Edited
20/01/2025

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Neurological Impairment (NI) can be any disorder of the body's nervous system and can present with a range of symptoms. Many children with NI are prone to chest infections, which can lead to long stays in hospital, and can be life-threatening. Despite the impact on children and their families due to these infections and the high cost to health services, there is very little information on how best to prevent them. Some doctors prescribe long-term antibiotics but it is not known whether this makes any difference to the number of chest infections children suffer from, or whether these antibiotics can cause long-term harm. This study is looking at an antibiotic called azithromycin and aims to find out whether 12 months of treatment with azithromycin reduces how often children with NI have to stay in hospital with chest infections.

Who can participate?
Children and young people with NI aged 3-17 years

What does the study involve?
If interested in participating in the study, the caregiver/young person or child will be asked to sign a consent/assent form to confirm this in writing. Once the form is signed, the caregiver will be asked some questions about their child's respiratory health and the site research team will check that the trial remains suitable before starting treatment. Before the participant starts their treatment of either azithromycin or placebo (dummy drug), information will be collected about them, including medical history and school attendance. Their weight will also be recorded and the caregiver will be asked to complete some questionnaires. Once the participant's treatment is dispensed, they will go home and complete the sleep assessment(s). After this has been completed the participant will start their treatment at home. The treatment will be given once daily every Monday, Wednesday and Friday for 12 months and neither the participant, their caregiver or the local clinical team looking after them will know if they are taking azithromycin or placebo. During the 12 months, the site research team will be in touch with the caregiver each month to ask how their child is getting on and if, for example, they have been to see their GP. Usually, this will be by phone or email, however, every 3 months this will be face-to-face so the site research team can provide the caregiver with more of their child's treatment, answer some

questionnaires and record their child's weight. The site research team will try to make these face-to-face follow-ups as easy as possible, for example, by arranging them at the same time as normal clinic visits where possible. There may be an additional face-to-face follow-up visit at 20 months, which will follow a similar format as the other face-to-face follow-up visits. If the participant does not take part in this additional visit, the site research team will ring the caregiver 28 days after their child finishes taking the treatment to check how their child has been since treatment stopped. In addition, if the participant visits their hospital outside of the arranged follow-up visits due to a chest infection, the site research team will also collect some information about this visit.

What are the possible benefits and risks of participating?
Azithromycin is used widely for the treatment of childhood infections. Children and young people who are given azithromycin may benefit from having fewer chest infections. There are very few side effects expected with azithromycin, though some children/young people may get mild diarrhoea and stomach pains and may feel sick (nausea) or be sick (vomit) when they first start taking azithromycin. Other side effects may include headache and feeling dizzy. There is a small chance that azithromycin may cause a rash or hearing problems. For those who are given the placebo there would be no higher risk than taking the antibiotics. If anyone who would like to take part is already taking antibiotics to prevent getting chest infections, then they would need to stop their antibiotics 13 weeks before entry into the trial. It is possible that during this period their respiratory symptoms might worsen. It is hoped that the results from the trial will help doctors and patients in the future when making decisions about treatment.

Where is the study run from?
University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
March 2019 to June 2024

Who is funding the study?
1. National Institute for Health Research HTA Programme (UK)
2. National Health and Medical Research Council (NHMRC) (Australia)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-001508-39

Integrated Research Application System (IRAS)
263255

Central Portfolio Management System (CPMS)
44576

Protocol serial number
ACTRN12619001597189, Grant Code: 16/17/01

Study information

Scientific 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 (the PARROT trial)

Acronym
PARROT

Study objectives
To determine whether 52 weeks of azithromycin prophylaxis is more effective than placebo in reducing the proportion of children and young people with non-progressive neurological impairment admitted to hospital with lower respiratory tract infections.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/03/2020, North West - Liverpool Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048387, +44 (0)207 104 8056; liverpoolcentral.rec@hra.nhs.uk), REC ref: 20/NW/0047

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Neurological impairment

Interventions
PARROT will be a joint UK and Australian multicentre trial. The primary objective is 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.

Study participants will be 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.

Taking part in the trial will involve phone or email follow-up every month and face-to-face visits every 3 months over a 12 month (52 week) period. Study tests include questionnaires, weight and nasal swabs*.

Initial visit will involve the assessment of eligibility criteria, including calculation of the LRSQ score, following consent. Once eligibility has been confirmed by a delegated medical practitioner, the patient can be randomised. The baseline visit will measure weight, assess if the patient is taking any concomitant medications and whether they have recently received any vaccinations and will review recent medical history. A series of questionnaires will be completed by the parent/caregiver and by the patient (if capacity allows). A nasal swab* will also be taken at this visit. Sleep actigraphy will be completed after randomisation, but prior to treatment administration. Study medication will be dispensed at this visit.

Participants will be contacted via email/phone at 1, 2, 4, 5, 7, 8, 10 and 11 months. An assessment of safety events, concomitant medication and changes to respiratory treatment and review of GP, A&E attendances and hospital admissions will be undertaken.

Participants will attend a face-to-face visit at 3, 6 and 9 months. In addition to the assessments performed at the email/phone visits, the parent/caregiver and participant (if capacity allows) will complete study questionnaires and return the completed treatment diary. The participants weight and relevant interventions will also be documented. Study medication will also be dispensed at these face-to-face visits. A nasal swab* will be taken at the 6-month visit.

Participants will also attend a face-to-face end of study visit at 12 months. In addition to the assessments performed at the face-face-visits, there will be a review of vaccinations and the sleep assessment(s) the parent/caregiver completed at the start of the study will be completed again just before this visit. This is also when treatment finishes and no more treatment will be dispensed. A nasal swab will also be taken at this visit*.

An additional face-to-face visit will take place at 20 months if recruitment to the trial is still ongoing. Assessments will be the same as those undertaken for the 12-month visit, excluding the sleep assessments and actigraphy. 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.

If a participant is hospitalised outside of their arranged follow-up visit due to a chest infection, additional information will be collected about this visit and a cough and nasal swab* will be collected.

Parents of children with neurological impairment were involved in all stages in the development of this trial. 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.

*As outlined in the protocol, swabs will be taken for Australian participants only. An amendment will be submitted to include swabs for UK participants once contractual arrangements are in place.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Proportion of children and young people (3-17 years) hospitalised* at their recruiting or designated centre with Lower Respiratory Tract Infection (LTRI) over the 52-week intervention period, recorded at 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks

*Hospitalisation includes those who are admitted to hospital for only a short period with LTRI 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

Key secondary outcome(s))
1. Health-related QoL of child and parent/carer measured using parent QoL assessment (Warwick-Edinburgh Mental Wellbeing Scale) and patient QoL assessment (DISABKIDS) at baseline, 13, 26, 39 and 52 weeks
2. Safety events, tolerability and adherence measured by the assessment of adverse events and withdrawals from study treatment at 4, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks, and treatment diary at 13, 26, 39 and 52 weeks
3. Respiratory medication usage assessed by reviewing concomitant medication which could impact the respiratory system at baseline, 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks, and vaccinations at baseline and 52 weeks
4. Weight based on World Health Organisation z-scores using WHO Anthro calculator (https://www.who.int/growthref/tools/en) assessed at baseline, 13, 26, 39 and 52 weeks
5. Quality/amount of parent and child/young person's sleep measured using the primary caregiver sleep actigraphy and corresponding primary caregiver sleep log (UK only), the Child's Sleep Habits Questionnaire and 1 week patient sleep diary at baseline and 52 weeks
6. Respiratory symptoms measured using LRSQ-Neuro score and the respiratory symptom questionnaire at baseline, 13, 26, 39 and 52 weeks, and changes to respiratory treatments /support and surgical/other interventions at 13, 26, 39 and 52 weeks
7. Number, duration and severity of LRTI; time to first LRTI is measured by reviewing the occurrence of chest infection and LRTI, changes to respiratory treatments/support and the assessment of adverse events at 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks; by using the resource use questionnaire at baseline, 13, 26, 39 and 52 weeks and documenting length of stay

in hospital, admission to PICU/HDU and changes to respiratory treatments/support for any unscheduled visits
8. Unscheduled medical presentations (GP visits and A&E attendances) for LRTI measured by reviewing medical history at baseline; reviewing the occurrence of chest infections and LRTIs and the assessment of adverse events at 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks, and using the resource use questionnaire at baseline, 13, 26, 39 and 52 weeks
9. Use of other health and social care services, school attendance and indirect costs measured using the resource use questionnaire at baseline, 13, 26, 39 and 52 weeks and Hospital Episode Statistics (HES) at 52 weeks
10. Number of courses of 'rescue' antibiotics prescribed for LRTI measured by reviewing concomitant medications which could impact the respiratory system at baseline, 4, 8, 13, 17, 21, 26, 30, 34, 39, 43, 47 and 52 weeks
11. Quality-adjusted life years (QALY) measured using CHU9D and EQ-5D-Y at baseline, 13, 26, 39 and 52 weeks
12. Nasal swab for microbiology and resistance profiling taken at baseline, 26 and 52 weeks, and for unscheduled visits (for Australian participants only until UK contractual arrangements are in place)
13. Nasal swab/nasopharyngeal aspirate to investigate viral causes of acute LRTI (as defined by the protocol) and cough swab/sputum collection to investigate bacterial causes of acute LRTI (as defined by the protocol) taken at unscheduled visits (for Australian participants only until UK contractual arrangements are in place)
14. Residual impact of 52 weeks antibiotic prophylaxis assessed at 78 weeks, using the following measures:
14.1. Respiratory symptoms measured by assessing LRSQ-Neuro score, respiratory symptom questionnaire, changes to respiratory treatments/support and surgical and other interventions
14.2. Weight based on World Health Organisation z-scores using WHO Anthro calculator (https://www.who.int/growthref/tools/en)
14.3. Nasal swab for microbiology and resistance profiling
14.4. Changes in respiratory medication usage measured by reviewing concomitant medications which could impact the respiratory system and vaccinations
14.5. Number, duration and severity of LRTI; time to first LRTI measured using the resource use questionnaire and reviewing the occurrence of chest infection and LRTI , changes to respiratory treatments/support and the collection of adverse events
14.6. Quality-adjusted life years (QALY) measured using the CHU9D and EQ-5D-Y
14.7. Use of other health and social care services, school attendance and indirect costs measured using Hospital Episode Statistics (HES)
14.8. Health-related QoL of child and parent/carer measured using the patient QoL assessment (DISABKIDS) and parent QoL assessment (Warwick-Edinburgh Mental Well-being Scale)
14.9. Unscheduled medical presentations (GP visits and A&E attendances) for LRTI measured by reviewing the occurrence of chest infection and LRTI, the collection of adverse events and the resource use questionnaire
14.10. Number of courses of 'rescue' antibiotics prescribed for LRTI measured by reviewing concomitant medications which could impact the respiratory system
14.11. Safety events measured using the assessment of adverse events

Completion date
04/06/2024

Eligibility

Key inclusion criteria

1. Children and young people who are aged between 3-17 years 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:
6.1. Received at least 2 courses of oral antibiotics for LRTI in 52 weeks prior to eligibility
6.2. Have been hospitalised with a LRTI within 52 weeks prior to eligibility and completed 13 week 'washout' period (where applicable)***
6.3. 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
*** 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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
3 years

Upper age limit
17 years

Sex
All

Total final enrolment
90

Key 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 or hypersensitivity to azithromycin, erythromycin, 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

Date of first enrolment
18/03/2022

Date of final enrolment
31/05/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Australia

Study participating centre
Alder Hey Children's NHS Foundation Trust
Alder Hey Hospital
Eaton Road
West Derby
Liverpool
United Kingdom
L12 2AP

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle-upon-Tyne
United Kingdom
NE7 7DN

Study participating centre
East London NHS Foundation Trust
9 Alie Street
Aldgate

London
United Kingdom
E1 8DE

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel
London
United Kingdom
E1 1BB

Study participating centre
NHS Grampian
Summerfield House
2 Eday Road
Aberdeen
United Kingdom
AB15 6RE

Study participating centre
NHS Tayside
Ninewells Hospital and Medical School
James Arrott Drive
Dundee
United Kingdom
DD1 9SY

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
NHS Lanarkshire
14 Beckford Street

Hamilton
United Kingdom
ML3 0TA

Study participating centre
County Durham and Darlington NHS Foundation Trust
Darlington Memorial Hospital
Hollyhurst Road
Darlington
United Kingdom
DL3 6HX

Study participating centre
South Tees Hospitals NHS Foundation Trust
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
North Tees and Hartlepool NHS Foundation Trust
University Hospital Of Hartlepool
Holdforth Road
Hartlepool
United Kingdom
TS24 9AH

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Wirral University Teaching Hospital NHS Foundation Trust
Arrowe Park Hospital
Arrowe Park Road
Upton

United Kingdom
CH49 5PE

Study participating centre
Countess Of Chester Hospital NHS Foundation Trust
The Countess Of Chester Health Park
Chester
United Kingdom
CH2 1UL

Study participating centre
Sheffield Children's NHS Foundation Trust
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
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United Kingdom
LS9 7TF

Study participating centre
Sherwood Forest Hospitals NHS Foundation Trust
Mansfield Road
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United Kingdom
NG17 4JL

Study participating centre
Nottingham University Hospitals NHS Trust
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NG7 2UH

Study participating centre
University Hospitals Of North Midlands NHS Trust
Newcastle Road
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
The Royal Wolverhampton NHS Trust
New Cross Hospital
Wolverhampton Road
Heath Town
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
St George's University Hospitals Nhs Foundation Trust
St George's Hospital
Blackshaw Road
Tooting
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United Kingdom
SW17 0QT

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
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United Kingdom
SE5 9RS

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
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Great Maze Pond
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SE1 9RT

Study participating centre
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Highpoint Venue
Bursledon Road
Southampton
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SO19 8BR

Study participating centre
Taunton and Somerset NHS Foundation Trust
Musgrove Park Hospital
Taunton
United Kingdom
TA1 5DA

Study participating centre
Birmingham Women's NHS Foundation Trust
Birmingham Womens Hospital
Metchley Park Road
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United Kingdom
B15 2TG

Study participating centre
University Hospitals Bristol and Weston NHS Foundation Trust
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Marlborough Street
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BS1 3NU

Study participating centre
University Hospitals of Derby and Burton NHS Foundation Trust
Royal Derby Hospital
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Derby
United Kingdom
DE22 3NE

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Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
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United Kingdom
OX3 9DU

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Bradford Royal Infirmary
Duckworth Lane
Bradford
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BD9 6RJ

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Lewsey Road
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LU4 0DZ

Study participating centre
Royal Free London NHS Foundation Trust
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Pond Street
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NW3 2QG

Study participating centre
Royal Devon and Exeter NHS Foundation Trust
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre

University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Northern Care Alliance NHS Foundation Trust
Salford Royal
Stott Lane
Salford
United Kingdom
M6 8HD

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

United Kingdom

Funder Name
National Health and Medical Research Council

Alternative Name(s)
National Health and Medical Research Council, Australian Government, NHMRC National Health and Medical Research Council, NHMRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Australia

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			20/01/2025	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes