NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

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ARCHIE
+44 (0)1865 617 842 • archie@phc.ox.ac.uk

Mrs Glenys Hunt
Chair, NRES Committee North West – Liverpool East
HRA NRES Centre Manchester
Barlow House, 3rd Floor
4 Minshull Street
Manchester
M1 3DZ
15 May 2017

Dear Mrs Hunt,

Study title: The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care (ARCHIE): a double-blind randomised placebo-controlled trial
REC reference: 13/NW/0621
Protocol number: ARCHIE001
EudraCT number: 2013-002822-21
IRAS project ID: 121769

With reference to the above study we would like to submit a substantial amendment SA017:

SA017 is an amendment to the protocol, changes are listed in appendix A:

Please find enclosed with this letter ARCHIE Protocol v3 as both a tracked and clean copy. IRAS form is also enclosed.

Tricia Carver
Senior Trial Manager
on behalf of Chief Investigator, Dr Kay Wang

Appendix A

1. Addition of investigator and updating of contact details
2. Clarified dosing regime based on BNF guidelines and addition of advice if child under 6kg
3. Clarified data collected during telephone follow up calls including compliance data
4. Addition of vaccination data collection in trial design summary as previously omitted in error
5. Modified eligibility criteria to:
    a. Remove requirement that children should be registered at a GP surgery in England and replaced with requirement that child should be registered at a GP surgery in UK.
    b. Clarify that exclusion criterion relating to antibiotic use within the last 72 hours refers specifically to use of antibiotics for treatment of acute infection.
    c. Clarify exclusion criteria relating to hospitalisation.
6. Addition of hospitalization with pneumonia as a potential risk category
7. Clarify recruitment and screening & eligibility processes to allow flexibility across different sites and site types.
8. Removal of term ‘high’ in reference to nasal swabs to better reflect actual procedure
9. Addition of availability of emergency randomization procedures
10. Changed reference to trial SOP’s to working instructions to reflect PC CTU internal policy that the term SOP's should be used to refer to general and trial procedures while work instructions should be used to refer to trial specific procedures.
11. Clarified SAE reporting procedures
12. Clarified extension of planned trial period to May 2019.

NHS
Health Research Authority

North West - Liverpool East Research Ethics Committee

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

13 June 2017

Ms Heather House
Oxford University NHS Trust
R&D Lead, Research and Development Department, Joint Research Office, Block 60, Churchill Hospital,
Oxford
Old Road
Headington
OX3 7LE

Dear Ms House

Study title:	**The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care(ARCHIE): a double-blind randomised placebo-controlled trial**
REC reference:	**13/NW/0621**
Protocol number:	**ARCHIE001**
EudraCT number:	**2013-002822-21**
Amendment number:	**17**
Amendment date:	**15 May 2017**
IRAS project ID:	**121769**

- Amendment to the protocol

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The sub-committee requested clarification on the emergency randomisation procedure. The researcher had responded explaining what the procedure entailed. The sub-committee were satisfied with the response.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter]		15 May 2017
Notice of Substantial Amendment (CTIMP) [Amendment Form]		15 May 2017
Other [Sponsor Approval Email]		15 May 2017
Research protocol or project proposal [Protocol - Clean]	3	19 April 2017
Research protocol or project proposal [Protocol - Tracked Changes]	3	19 April 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

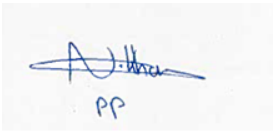
The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

13/NW/0621:	**Please quote this number on all correspondence**

Yours sincerely



On Behalf Of
Mrs Glenys J Hunt
Chair

E-mail: nrescommittee.northwest-liverpooleast@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Mark Dolman, NIHR Clinical Research Network: Thames Valley and South Midlands*
Dr Kay Wang, University of Oxford

North West - Liverpool East Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 22 May 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mrs Glenys J Hunt	Solicitor	Yes	Chair
Miss Kimberley Saint	Clinical Scientist - Nuclear Medicine	Yes	

Sharon Tonner

From: ROBINSON, Jade (HEALTH RESEARCH AUTHORITY) <jade.robinson1@nhs.net>
Sent: 13 June 2017 14:04
To: Primary Health Care Archie
Cc: Kay Wang; TMA, Ouh (OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST); CTRG Sponsorship Correspondence; Karl Shepherd; studysupport.crnthamesvalley@nihr.ac.uk
Subject: RE: IRAS 121769 - Substantial Amendment 17 - Assessment of Amendment Complete

Follow Up Flag: Flag for follow up
Flag Status: Flagged

Dear Silviya

Further to the below, I am pleased to confirm that HRA Approval has been issued for the referenced amendment, following assessment against the HRA criteria and standards.

The sponsor should now work collaboratively with participating NHS organisations in England to implement the amendment as per the below categorisation information. This email may be provided by the sponsor to participating organisations in England to evidence that the amendment has HRA Approval.

Please contact hra.amendments@nhs.net for any queries relating to the assessment of this amendment.

Kind regards

Jade

Jade Robinson | Amendment Coordinator – North East REC Centre
Health Research Authority
Room 001. Jarrow Business Centre, Rolling Mill, Jarrow, Tyne & Wear

If you have any queries please email the address below:
E: hra.amendments@nhs.net | T: 0207 104 8089

www.hra.nhs.uk

IMPORTANT – **Click here** for details of significant changes to the REC booking and submission process

The HRA is keen to know your views on the service you received – our short feedback form is available **here**

If your email is regarding a formal request for information under the Freedom of Information Act, please resend to HRA.FOI@nhs.net to ensure it is dealt with promptly

Help save paper - do you need to print this email?

From: nrescommittee.northwest-liverpooleast@nhs.net [mailto:nrescommittee.northwest-liverpooleast@nhs.net]
Sent: 22 May 2017 15:16
To: archie@phc.ox.ac.uk
Cc: kay.wang@phc.ox.ac.uk; ouhtma@nhs.net; ctrg@admin.ox.ac.uk; karl.shepherd@admin.ox.ac.uk; studysupport.crnthamesvalley@nihr.ac.uk
Subject: IRAS 121769. Confirmation of REC Validation and Categorisation of Amendment

Dear Silviya

IRAS Project ID:	**121769**
REC Reference:	**13/NW/0621**
Short Study Title:	**The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE**
Date complete amendment submission received:	**15 May 2017**
Amendment No./ Sponsor Ref:	
Amendment Date:	**15 May 2017**
Amendment Type:	**Substantial**

Thank you for submitting the above referenced amendment. I am pleased to confirm that this amendment has been submitted to the REC for ethical review. Please find attached a copy of the validation letter.

Categorisation of Amendment

In line with the UK Process for Handling UK Study Amendments I can confirm that this amendment has been categorised as:

- **Category A -** An amendment that has implications for, or affects, ALL participating NHS organisations

You should now provide this email, together with the amended documentation, to the research management support offices **and** local research teams at your participating NHS organisations in England.

If you have participating NHS organisations in Northern Ireland, Scotland and/or Wales, you should communicate directly with the relevant research teams to prepare them for implementing the amendment, as per the instructions below. You do not need to provide this email or your amended documentation to their research management support offices, as we will pass these to the relevant national coordinating functions who will do this on your behalf.

Subject to the three conditions below, you will be able to implement the amendment at your participating NHS organisations in England **35 days after you notify them of the amendment.** A template email to notify participating NHS organisations in England is provided here.

- You may not implement this amendment until and unless you receive all required regulatory approvals, including REC favourable opinion, (for participating organisations in England, this includes receiving confirmation of HRA Approval for the amendment). You should provide regulatory approvals to the research management support offices and local research teams at your participating NHS organisations in England, plus to local research teams at any participating NHS organisations in Northern Ireland, Scotland or Wales*.
- You may not implement this amendment at any participating NHS organisations which inform you within the 35 day period that they require additional time to consider the amendment, until they notify you that the considerations have been satisfactorily completed.

- You may not implement this amendment at any participating NHS organisation that informs you that it is no longer able to undertake this study.

Note: you may only implement changes described in the amendment notice or letter.

If you receive required regulatory approvals (for participating organisations in England, this includes confirmation that the amendment has been granted HRA Approval) after the 35 days have passed, you may then immediately implement this amendment at all participating NHS organisations that have not requested additional review time, or are no longer able to undertake this study.

There is no need for you to receive a letter of confirmation from the participating organisation that the amendment can be implemented, as the intended date of implementation is communicated through the above process. However, you may be able to implement this amendment ahead of the 35 day deadline, if all necessary regulatory approvals are in place and the participating organisation has confirmed that the amendment may be implemented ahead of the 35 day date.

* Where the study involves NHS organisations in Northern Ireland, Scotland or Wales, the HRA will forward regulatory approvals to the relevant national coordinating function to distribute to their research management support offices.

Please do not hesitate to contact me if you require further information.

Kind regards

Nafeesa Khanam

REC Assistant

Health Research Authority
HRA, Ground Floor, Skipton House, 80 London Road, London, SE1 6LH
E: hra.amendments@nhs.net

www.hra.nhs.uk

The HRA is keen to know your views on the service you received – our short feedback form is available here

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****

Primary Health Care Archie

From: nrescommittee.northwest-liverpooleast@nhs.net
Sent: 22 May 2017 15:16
To: Primary Health Care Archie
Cc: Kay Wang; ouhtma@nhs.net; CTRG Sponsorship Correspondence; Karl Shepherd; studysupport.crnthamesvalley@nihr.ac.uk
Subject: IRAS 121769. Confirmation of REC Validation and Categorisation of Amendment
Attachments: 13 NW 0621 IRAS 121769 Ack Valid Sub Amend 17 .pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Silviya

IRAS Project ID:	**121769**
REC Reference:	**13/NW/0621**
Short Study Title:	**The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE**
Date complete amendment submission received:	**15 May 2017**
Amendment No./ Sponsor Ref:	
Amendment Date:	**15 May 2017**
Amendment Type:	**Substantial**

Thank you for submitting the above referenced amendment. I am pleased to confirm that this amendment has been submitted to the REC for ethical review. Please find attached a copy of the validation letter.

Categorisation of Amendment

In line with the UK Process for Handling UK Study Amendments I can confirm that this amendment has been categorised as:

- **Category A -** An amendment that has implications for, or affects, ALL participating NHS organisations

You should now provide this email, together with the amended documentation, to the research management support offices **and** local research teams at your participating NHS organisations in England.

If you have participating NHS organisations in Northern Ireland, Scotland and/or Wales, you should communicate directly with the relevant research teams to prepare them for implementing the amendment, as per the instructions below. You do not need to provide this email or your amended documentation to their research management support offices, as we will pass these to the relevant national coordinating functions who will do this on your behalf.

Subject to the three conditions below, you will be able to implement the amendment at your participating NHS organisations in England **35 days after you notify them of the amendment.** A template email to notify participating NHS organisations in England is provided here.

- You may not implement this amendment until and unless you receive all required regulatory approvals, including REC favourable opinion, (for participating organisations in England, this includes receiving confirmation of HRA Approval for the amendment). You should provide regulatory approvals to the research management support offices and local research teams at your participating NHS organisations in England, plus to local research teams at any participating NHS organisations in Northern Ireland, Scotland or Wales*.

- You may not implement this amendment at any participating NHS organisations which inform you within the 35 day period that they require additional time to consider the amendment, until they notify you that the considerations have been satisfactorily completed.
- You may not implement this amendment at any participating NHS organisation that informs you that it is no longer able to undertake this study.

Note: you may only implement changes described in the amendment notice or letter.

If you receive required regulatory approvals (for participating organisations in England, this includes confirmation that the amendment has been granted HRA Approval) after the 35 days have passed, you may then immediately implement this amendment at all participating NHS organisations that have not requested additional review time, or are no longer able to undertake this study.

There is no need for you to receive a letter of confirmation from the participating organisation that the amendment can be implemented, as the intended date of implementation is communicated through the above process. However, you may be able to implement this amendment ahead of the 35 day deadline, if all necessary regulatory approvals are in place and the participating organisation has confirmed that the amendment may be implemented ahead of the 35 day date.

* Where the study involves NHS organisations in Northern Ireland, Scotland or Wales, the HRA will forward regulatory approvals to the relevant national coordinating function to distribute to their research management support offices.

Please do not hesitate to contact me if you require further information.

Kind regards

Nafeesa Khanam

REC Assistant

Health Research Authority
HRA, Ground Floor, Skipton House, 80 London Road, London, SE1 6LH
E: hra.amendments@nhs.net

www.hra.nhs.uk

The HRA is keen to know your views on the service you received – our short feedback form is available here

Sharon Tonner

From: Elaine Chick
Sent: 15 May 2017 13:25
To: Sharon Tonner
Cc: 'rpm@oxfordjro.org'
Subject: ARCHIE study substantial amendment 17

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Sharon

Thank you for your substantial amendment submission.

I can confirm that the above referenced substantial amendment has been reviewed in CTRG and we are happy for it to be submitted to REC, host organisation and HRA for approval. This email can be forwarded to the REC as confirmation of sponsor approval for the amendment.

In order to ensure validation of your submission by the REC, send them both tracked and clean copies of all amended documents.

- Email documents to the REC that originally reviewed the study. The REC will transfer the amendment internally to HRA for them to review and categorise. HRA will advise you when you can send final REC and HRA approved documents to your local sites.

- Copy in CTRG administrator (karl.shepherd@admin.ox.ac.uk) so the Sponsor has final documents and is included in subsequent correspondence

Please send Karl karl.shepherd@admin.ox.ac.uk a copy of the REC opinion letter, HRA approval letter once you have received them. Please do not implement your amendment until all approvals are in place.

Please remember to update your entry on the Clinicaltrials.gov website or equivalent if relevant.

Kind regards,
Elaine

PID8801-A027-SP001-AC001

Elaine Chick
Deputy Head of CTRG | Research Services
University of Oxford
Joint Research Office, Churchill Hospital, Oxford, OX3 7LE
T: +44 01865 572222
www.admin.ox.ac.uk/researchsupport/ctrg

Please note I usually work Mon-Thurs only

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

(●) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
( ) Basic science study involving procedures with human participants
( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

( ) Yes (●) No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA? ○ Yes ◉ No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product? ○ Yes ◉ No

2e. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ○ Yes ◉ No

b) Will you be taking new human tissue samples (or other human biological samples)? ◉ Yes ○ No

c) Will you be using existing human tissue samples (or other human biological samples)? ○ Yes ◉ No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- ☑ England
- ☐ Scotland
- ☐ Wales
- ☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

- ☐ IRAS Form
- ☑ NHS/HSC Research and Development offices
- ☐ Social Care Research Ethics Committee
- ☑ Research Ethics Committee
- ☑ Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- ☐ Gene Therapy Advisory Committee (GTAC)
- ☐ Confidentiality Advisory Group (CAG)
- ☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

5. Will any research sites in this study be NHS organisations?

(●) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

(●) Yes ( ) No

Please see information button for further details.

6. Do you plan to include any participants who are children?

(●) Yes ( ) No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

( ) Yes (●) No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

( ) Yes (●) No

9. Is the study or any part of it being undertaken as an educational project?

( ) Yes (●) No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

( ) Yes (●) No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

( ) Yes (●) No

SUBSTANTIAL AMENDMENT FORM [1]

NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION

For official use:

Date of receiving the request:	Grounds for non acceptance/negative opinion:
	Date:
Date of start of procedure:	Authorisation/ positive opinion:
	Date:
Competent authority registration number of the trial:	Withdrawal of amendment application:
Ethics committee registration number of the trial:	Date:

To be filled in by the applicant:

*This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.*

A TYPE OF NOTIFICATION

A.1 Member State in which the substantial amendment is being submitted:

United Kingdom

A.2 Notification for authorisation to the competent authority: ☐

A.3 Notification for an opinion to the ethics committee: ☑

(1) Cf. Section 3.7.b of the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (OJ, C82, 30.3.2010, p.1) hereinafter referred to as 'detailed guidance CT-1'.

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1 Does the substantial amendment concern several trials involving the same IMP? [2] ○ Yes ◉ No

B.2 EudraCT number:	2013-002822-21
B.3 Full title of the trial:	The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care (ARCHIE): a double-blind randomised placebo-controlled trial
B.4 Sponsor's protocol code number:	ARCHIE001
B.4 Sponsor's protocol version number:	v2
B.4 Sponsor's protocol date:	12/02/2014

(2) Cf. Section 3.7. of the detailed guidance CT-1

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1 Sponsor

Organisation:	University of Oxford
Contact Given name:	Heather
Contact Family name:	House
Address:	Joint Research Office, Block 60, Churchill Hospital
Town/city:	Headington, Oxford
Post code:	OX3 7LE
Telephone:	
Fax:	01865572228
E-mail:	ctrg@admin.ox.ac.uk

C.2 Legal representative [3] of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)

Name of organisation:
Contact Given name:
Contact Family name:
Address:
Town/city:
Post code:
Telephone:
Fax:
E-mail:

(3) As stated in Article 19 of Directive 2001/20/EC.

D APPLICANT IDENTIFICATION, (please tick the appropriate box)

D1. Request for the competent authority

D.1.1 Sponsor ☐
D.1.2 Legal representative of the sponsor ☐
D.1.3 Person or organisation authorised by the sponsor to make the application. ☐
D.1.4 Complete below:

Name of organisation
Contact Given name
Contact Family name
Address
Town/city
Post code

Telephone
Fax
E-mail

D2. Request for the Ethics Committee

D.2.1 Sponsor ☐
D.2.2 Legal representative of the sponsor ☐
D.2.3 Person or organisation authorised by the sponsor to make the application. ☑
D.2.4 Investigator in charge of the application if applicable[4]:
- Co-ordinating investigator (for multicentre trial): ☐
- Principal investigator (for single centre trial): ☐

D.2.5 Complete below:

Name of organisation	University of Oxford
Given name	Tricia
Family name	Carver
Address	Nuffield Department of Primary Care Health Sciences
Town/city	
Post code	OX26GG
Telephone	01865617842
Fax	
E-mail	tricia.carver@phc.ox.ac.uk

(4) According to national legislation.

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1 Sponsor's substantial amendment information for the clinical trial concerned:

Code Number: ARCHIE_SA17
Version:
Date: 2017/04/19

E.2 Type of substantial amendment

E.2.1 Amendment to information in the CT application form	○ Yes	◉ No
E.2.2 Amendment to the protocol	◉ Yes	○ No
E.2.3 Amendment to other documents appended to the initial application form	○ Yes	◉ No

If yes specify:

E.2.4 Amendment to other documents or information: ○ Yes ◉ No

If yes specify:

E.2.5 This amendment concerns mainly urgent safety measures already implemented[5]:	○ Yes	◉ No
E.2.6 This amendment is to notify a temporary halt of the trial[6]:	○ Yes	◉ No
E.2.7 This amendment is to request the restart of the trial[7]:	○ Yes	◉ No

(5) Cf. Section 3.9. of the detailed guidance CT-1.
(6) Cf. Section 3.10. of the detailed guidance CT-1
(7) Cf. Section 3.10. of the detailed guidance CT-1

E.3 Reasons for the substantial amendment:

E.3.1 Changes in safety or integrity of trial subjects	○ Yes	◉ No
E.3.2 Changes in interpretation of scientific documents/value of the trial	○ Yes	◉ No
E.3.3 Changes in quality of IMP(s)	○ Yes	◉ No
E.3.4 Changes in conduct or management of the trial	◉ Yes	○ No
E.3.5 Change or addition of principal investigator(s), co-ordinating investigator	○ Yes	◉ No
E.3.6 Change/addition of site(s)	○ Yes	◉ No
E.3.7 Other change	○ Yes	◉ No
E.3.7.1 If yes specify:		
E.3.8 Other case	○ Yes	○ No
E.3.8.1 If yes specify:		

E.4 Information on temporary halt of trial:[8]

E.4.1 Date of temporary halt		
E.4.2 Recruitment has been stopped	○ Yes	○ No
E.4.3 Treatment has been stopped	○ Yes	○ No

E.4.4 Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment

E.4.5 Briefly describe:

Justification for a temporary halt of the trial *(free text)*:

The proposed management of patients receiving treatment at time of the halt *(free text)*:

The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text)*:

(8) Cf. Section 3.10. of the detailed guidance CT-1

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9]

Please use this section to detail each substantial amendment which is being notified. If you are notifying more than one substantial amendment, please use the "Add Amendment" button as required

Substantial amendment 1

Previous and new wording:*(tracked)*

N/A - addition of investigator, Professor Christopher Butler, University of Oxford and updated contact details

New wording:

Comments/ explanation/ reasons for substantial amendment:

Addition of investigator (Prof C Butler, University of Oxford)and updated contact details

Substantial amendment 2

Previous and new wording:*(tracked)*

Dose: Health care professionals will use their clinical judgement when advising on study medication doses in any children to whom it is felt that the standard British National Formulary (BNF) dosing recommendations should not apply.

Child's age	Study medication dose
6 months to 23 months • **Under 6 kg**	**Calculate dose accordingto BNF instructions for co-amoxiclav 400/57. Advise two doses daily for 5 days**
• 6.0 – 7.9 kg	1 ml twice daily for 5 days
• 8.0 – 10.9 kg	1.5 ml twice daily for 5 days
• 11.0 – 12.9 kg	2 ml twice daily for 5 days
2 to 6 years	2.5 ml twice daily for 5 days
7 to 12 years	5 ml twice daily for 5 days

New wording:

Dose: Health care professionals will use their clinical judgement when advising on study medication doses in any children to whom it is felt that the standard British National Formulary (BNF) dosing recommendations should not apply.

Child's age Study medication dose
6 months to 23 months
• Under 6 kg
Calculate dose according to BNF instructions for co-amoxiclav 400/57. Advise two doses daily for 5 days
• 6.0 – 7.9 kg 1 ml twice daily for 5 days
• 8.0 – 10.9 kg 1.5 ml twice daily for 5 days
• 11.0 – 12.9 kg 2 ml twice daily for 5 days
2 to 6 years 2.5 ml twice daily for 5 days
7 to 12 years 5 ml twice daily for 5 days

Comments/ explanation/ reasons for substantial amendment:

Clarified dosing regime based on BNF guidelines and addition of advice if child under 6kg

Substantial amendment 3

Previous and new wording:*(tracked)*

An appropriately trained healthcare professional or member of the research team will contact the parents/guardians of trial participants one week and two weeks after study entry to record data on health service contacts~~ and~~ adverse events, **duration of fever, medication compliance,** and to remind parents/guardians to complete their study diaries and questionnaires. (p18)

A healthcare professional or a member of the research team will arrange telephone follow-up calls after one week (between day 7 and day 10) and two weeks (between day 14 and day 17). ~~As well as~~ Text, e-mail or telephone reminders on days 4, 21 and 28 **may also be agreed.**

At the week 1 and week 2 telephone follow-ups, a healthcare professional/researcher will ask parents/guardians about **health service contacts, adverse events, duration of fever, medication compliance** ~~health care service contacts and adverse events~~, and remind them to complete their study diaries and questionnaires. (~~parents/guardians: EQ-5D-Y proxy and CARIFS on day 7, EQ-5D-Y proxy on day 14; children: EQ-5D-Y on days 7 and 14).~~ Adverse events will be reported to the PC-CTU. Text or e-mail reminders ~~will~~ **may** replace the week 1 and week 2 telephone follow-ups if these do not take place or cannot be scheduled. (p25)

Parents or guardians will be asked to record in their study diaries each dose of study medication given to the child. **Compliance data will also be collected on either the 1 or 2 week follow-up CRF.** Children whose study diaries indicate that they received 8 or more doses of study medication from days 1 to 6 inclusive will be considered to be compliant with study medication. All randomised trial participants will be included in the intention-to treat population. (p27)

New wording:

An appropriately trained healthcare professional or member of the research team will contact the parents/guardians of trial participants one week and two weeks after study entry to record data on health service contacts, and adverse events, duration of fever, medication compliance, and to remind parents/guardians to complete their study diaries and questionnaires. (p18)

A healthcare professional or a member of the research team will arrange telephone follow-up calls after one week (between day 7 and day 10) and two weeks (between day 14 and day 17). Text, e-mail or telephone reminders on days 4, 21 and 28 may also be agreed.
At the week 1 and week 2 telephone follow-ups, a healthcare professional/researcher will ask parents/guardians about health service contacts, adverse events, duration of fever, medication compliance, and remind them to complete their study diaries and questionnaires. Adverse events will be reported to the PC-CTU. Text or e-mail reminders may replace the week 1 and week 2 telephone follow-ups if these do not take place or cannot be scheduled. (p25)

Parents or guardians will be asked to record in their study diaries each dose of study medication given to the child. Compliance data will also be collected on either the 1 or 2 week follow-up CRF. Children whose study diaries indicate that they received 8 or more doses of study medication from days 1 to 6 inclusive will be considered to be compliant with study medication. All randomised trial participants will be included in the intention-to treat population. (p27)

Comments/ explanation/ reasons for substantial amendment:

Clarified data collected during telephone follow up calls including compliance data

Substantial amendment 4

Previous and new wording:*(tracked)*

A healthcare professional or member of the research team will extract data from each child's medical record on consultations which occurred during the 12-month period before study entry, **vaccinations**, antibiotics prescribed during the 3-month period before study entry and investigations, medications prescribed, hospitalisations and consultations with clinicians in primary care or other equivalent ambulatory care settings during the 28-day period

after study entry.

New wording:

A healthcare professional or member of the research team will extract data from each child's medical record on consultations which occurred during the 12-month period before study entry, vaccinations, antibiotics prescribed during the 3-month period before study entry and investigations, medications prescribed, hospitalisations and consultations with clinicians in primary care or other equivalent ambulatory care settings during the 28-day period after study entry.

Comments/ explanation/ reasons for substantial amendment:

Addition of vaccination data collection in trial design summary as previously omitted in error

Substantial amendment 5

Previous and new wording:*(tracked)*

Inclusion Criteria

- Aged 6 months to 12 years inclusive.
- In 'at risk' category*.
- Presenting with influenza-like illness (i.e. cough and fever**) during influenza season.
- Presenting within 5 days of symptom onset.
- Permanently registered at a general practice in ~~England~~ **UK**
- Parent /guardian able to complete study diary and questionnaires.

Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Known contraindication to co-amoxiclav ***.
- Child given antibiotics **for treatment of an acute infection** within the last 72 hours.
- Child requires immediate antibiotics ~~or hospital admission~~ (clinician's judgement).
- **Child requires immediate hospital admission for treatment of an influenza-related complication (clinician's judgement).**
- **Child has been observed on hospital ward or ambulatory care unit for longer than 24 hours**.
- Presence of any reason to prevent healthcare professional from obtaining ~~high~~ nasal swab.
- Child with known cystic fibrosis.
- Child previously entered into the ARCHIE study.
- Child has been involved in another medicinal trial within the last 90 days.

New wording:

Inclusion Criteria
• Aged 6 months to 12 years inclusive.
• In 'at risk' category*.
• Presenting with influenza-like illness (i.e. cough and fever**) during influenza season.
• Presenting within 5 days of symptom onset
• Permanently registered at a general practice in UK
• Parent /guardian able to complete study diary and questionnaires.
Exclusion Criteria
The participant may not enter the trial if ANY of the following apply:
• Known contraindication to co-amoxiclav ***.
• Child given antibiotics for treatment of an acute infection within the last 72 hours.
• Child requires immediate antibiotics (clinician's judgement).
• Child requires immediate hospital admission for treatment of an influenza-related complication (clinician's judgement).
• Child has been observed on hospital ward or ambulatory care unit for longer than 24 hours.
• Presence of any reason to prevent healthcare professional from obtaining nasal swab.

• Child with known cystic fibrosis.
• Child previously entered into the ARCHIE study.
• Child has been involved in another medicinal trial within the last 90 days.

Comments/ explanation/ reasons for substantial amendment:

Clarify inclusion/exclusion criteria and removal of need for GP registered in England only

Substantial amendment 6

Previous and new wording:*(tracked)*

Admitted to hospital with bronchiolitis **or pneumonia** within the last 12 months.

New wording:

Admitted to hospital with bronchiolitis or pneumonia within the last 12 months.

Comments/ explanation/ reasons for substantial amendment:

Addition of hospitalisation with pneumonia as a potential risk category

Substantial amendment 7

Previous and new wording:*(tracked)*

We will recruit study participants from a range of health care settings where 'at risk' children from the community present with influenza-like illness. Recruiting sites will include general practices, walk-in centres and hospitals. Identification of participants at these sites may be supported by the use of participant identification centres. Baseline assessments and follow-up swabs may be conducted either at the recruiting site or in participants' homes.

Where possible, recruitment sites will be asked to perform database searches to identify children in 'at risk' groups before each recruitment season.

To raise awareness about the trial and opportunities for participation, we will provide a short information ~~pre season~~ **leaflet** ~~to inform the parents/guardians of these children about the study~~**, which may be distributed by post, e-mail or at sites themselves to inform parents/guardians of 'at risk' children about the study.** The leaflet will offer parents/guardians the opportunity to register their interest in the study ~~with the research team. The research team will inform the site of children whose parents/guardians register an interest in the study and ask them to put an alert on the medical records of these children. The alert will indicate that these children and their parents/guardian have been informed about the study and registered an interest in taking part. Parents/guardians will also be able to register interest directly with the site.~~ Recruiting sites **and participation identification centres** will **also** be provided with **other** promotional study materials such as posters, ~~short version participant information leaflets~~ and ~~interest~~ cards.

T**he study may also be publicised via local news outlets, social media, charities working with relevant patient groups and the study website. Parents who express an interest in allowing their child to take part in the study will be able to contact the study team or look at the study website to find their nearest recruiter.** (p20-21)

Participants will be assessed against the eligibility criteria listed in section 7. ~~If there is a delay between introduction of the study/eligibility assessment and consent/randomization, then the recruiter must confirm all eligibility criteria are still met. This is documented on the baseline assessment.~~

A medically qualified individual or appropriately qualified nurse practitioner at the participating site will assess the child's eligibility for study inclusion. If informed consent, baseline assessment procedures and randomisation are to be completed by a different health care professional in the child's home, this should be done within 24 hours of eligibility being confirmed. If a health care professional is concerned that the child no longer meets study eligibility criteria at the time of the home visit, they should not recruit the child and seek medical advice. (p22)

New wording:

We will recruit study participants from a range of health care settings where 'at risk' children from the community present with influenza-like illness. Recruiting sites will include general practices, walk-in centres and hospitals. Identification of participants at these sites may be supported by the use of participant identification centres. Baseline assessments and follow-up swabs may be conducted either at the recruiting site or in participants' homes.
Where possible, recruitment sites will be asked to perform database searches to identify children in 'at risk' groups before each recruitment season.
To raise awareness about the trial and opportunities for participation, we will provide a short information leaflet, which may be distributed by post, e-mail or at sites themselves to inform parents/guardians of 'at risk' children about the study. The leaflet will offer parents/guardians the opportunity to register their interest in the study. Recruiting sites and participation identification centres will also be provided with other promotional study materials such as posters and cards.

The study may also be publicised via local news outlets, social media, charities working with relevant patient groups and the study website. Parents who express an interest in allowing their child to take part in the study will be able to contact the study team or look at the study website to find their nearest recruiter. (P20-21)

Participants will be assessed against the eligibility criteria listed in section 7. A medically qualified individual or appropriately qualified nurse practitioner at the participating site will assess the child's eligibility for study inclusion. If informed consent, baseline assessment procedures and randomisation are to be completed by a different health care professional in the child's home, this should be done within 24 hours of eligibility being confirmed. If a health care professional is concerned that the child no longer meets study eligibility criteria at the time of the home visit, they should not recruit the child and seek medical advice. (p22)

Comments/ explanation/ reasons for substantial amendment:

Clarify recruitment and screening & eligibility processes to allow flexibility across different sites and site types.

Substantial amendment 8

Previous and new wording:*(tracked)*

Presence of any reason to prevent healthcare professional from obtaining ~~high~~ nasal swab (p19)

~~A high~~ nasal swab for real-time Polymerase Chain Reaction (PCR) analysis to detect influenza and distinguish influenza A, B and A/H1N1 2009 pandemic subtypes. (P23)

New wording:

Presence of any reason to prevent healthcare professional from obtaining nasal swab (p19)

A nasal swab for real-time Polymerase Chain Reaction (PCR) analysis to detect influenza and distinguish influenza A, B and A/H1N1 2009 pandemic subtypes. (P23)

Comments/ explanation/ reasons for substantial amendment:

Removal of term 'high' in reference to nasal swabs to better reflect actual procedure

Substantial amendment 9

Previous and new wording:*(tracked)*

The healthcare professional recruiting the child will use a web-based randomisation system. Randomisation will be stratified by region with minimisation for age (< 2 or ≥ 2 years old) and current seasonal influenza vaccination status (yes or no/don't know). The randomisation system will be implemented and managed by the PC-CTU. **An emergency backup randomisation procedure will be available supported by the trial office.**

New wording:

The healthcare professional recruiting the child will use a web-based randomisation system. Randomisation will

be stratified by region with minimisation for age (< 2 or ≥ 2 years old) and current seasonal influenza vaccination status (yes or no/don't know). The randomisation system will be implemented and managed by the PC-CTU. An emergency backup randomisation procedure will be available supported by the trial office.

Comments/ explanation/ reasons for substantial amendment:

Addition of availability of emergency randomization procedures referenced.

Substantial amendment 10

Previous and new wording:*(tracked)*

Procedures for unblinding of the randomisation code will be described in a Trial Specific ~~SOP's~~ **work instructions** and include arrangements for an independent custodian of the randomisation codes to be appointed and access in working hours to individual codes from the independent custodian or their representative by the Chief Investigator or a designated named clinician.

New wording:

Procedures for unblinding of the randomisation code will be described in a Trial Specific work instructions and include arrangements for an independent custodian of the randomisation codes to be appointed and access in working hours to individual codes from the independent custodian or their representative by the Chief Investigator or a designated named clinician.

Comments/ explanation/ reasons for substantial amendment:

Changed reference to trial SOP's to working instructions to reflect PC CTU internal policy that the term SOP's should be used to refer to general and trial procedures while work instructions should be used to refer to trial specific procedures.

Substantial amendment 11

Previous and new wording:*(tracked)*

All SAEs will be reported using the PC-CTU SAE Report form **which provides reporting directions.** ~~The PC-CTU will maintain dedicated report lines with answerphone and fax facilities to allow reporting of SAE's.~~ The answerphone, **emails** and fax will be checked regularly during office hours.

New wording:

All SAEs will be reported using the PC-CTU SAE Report form which provides reporting directions. The answerphone, emails and fax will be checked regularly during office hours.

Comments/ explanation/ reasons for substantial amendment:

Clarified SAE reporting procedures

Substantial amendment 12

Previous and new wording:*(tracked)*

Planned Trial Period	October 2013 to ~~March~~ **May** ~~2017~~ **2019** inclusive

New wording:

Planned Trial Period October 2013 to May 2019 inclusive

Comments/ explanation/ reasons for substantial amendment:

Clarified extension of planned trail period to May 2019.

(9) Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

Type of change:

G.1.1 Addition of a new site

G.1.1.1 Principal investigator (provide details below)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)
Professional address

G.1.2 Removal of an existing site

G.1.2.1 Principal investigator (provide details below)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)
Professional address

G.1.3 Change of co-ordinating investigator (provide details below of the new coordinating investigator)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)
Professional address

G.1.3.6 Indicate the name of the previous co-ordinating investigator:

G.1.4 Change of principal investigator at an existing site (provide details below of the new principal investigator)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)

Professional address

G.1.4.6 Indicate the name of the previous principal investigator:

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

H.1 Change of e-mail contact for feedback on application*

H.2 Change to request to receive an .xml copy of CTA data ○ Yes ◉ No

H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? ○ Yes ◉ No

H.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):

H.2.2 Do you want to receive this via password protected link(s)[10]? ○ Yes ◉ No

If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s)

H.2.3 Do you want to stop messages to an email for which they were previously requested? ○ Yes ◉ No

H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:

(*This will only come into effect from the time at which the request is processed in EudraCT).

(10) This requires a EudraLink account. (See eudract.emea.europa.eu for details)

I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

I.1 Cover letter ☑

I.2 Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form) ☐

I.3 Entire new version of the document[11] ☑

I.4 Supporting information ☐

I.5 Revised .xml file and copy of initial application form with amended data highlighted ☐

I.6 Comments on any novel aspect of the amendment if any :

(11) Cf. Section 3.7.c. of the detailed guidance CT-1

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

J.1 I hereby confirm that/ confirm on behalf of the sponsor that (delete which is not applicable)

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY*(as stated in section D.1):* ☐

J.2.1 Signature [12]: .....

J.2.2 Print name:

J.2.3 Date:

J.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE *(as stated in section D.2)***:** ☐

J.3.1 Signature [13]: .....

J.3.2 Print name:

J.3.3 Date:

This section was signed electronically by Mrs Tricia Carver on 15/05/2017 14:08.

Job Title/Post:

Organisation:

Email: tricia.carver@phc.ox.ac.uk

(12) On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
(13) On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.

Trial Title: The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care (ARCHIE): a double-blind randomised placebo-controlled trial

Short title: The early use of Antibiotics in at Risk Children with InfluEnza (ARCHIE)

Department Internal Reference Number: KW/ARCHIE/0009

Sponsor's Protocol Code Number: ARCHIE001

Ethics Ref: 13/NW/0621

EudraCT Number: 2013-002822-21

Date and Version No: 12 19 April February 20147 v3

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Sponsor: University of Oxford

Funder: National Institute for Health Research (NIHR), Programme Grants for Applied Research (PGfAR)

RP-PG-1210-12012

Chief Investigator Signature:

No potential conflicts of interest to be declared.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. KEY TRIAL CONTACTS

Chief Investigator	Dr Kay Wang University of Oxford Nuffield Department of Primary Care Health Sciences Radcliffe Observatory Quarter Woodstock Road, Oxford, OX2 6GG, UK 01865 289312 (Tel) 01865 289412 (Fax) Email: kay.wang@phc.ox.ac.uk
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Statistician	Ly-Mee Yu Clinical Trials Unit Radcliffe Observatory Quarter Woodstock Road Oxford, OX2 6GG~~Nuffield Department of Primary Care Health Sciences~~ ~~University of Oxford~~ ~~23-38 Hythe Bridge Street~~ ~~Oxford OX1 2ET~~ Direct line: 01865 617199 FAX: 01865 289 412 Email: ly-mee.yu@phc.ox.ac.uk

Committees	ARCHIE Programme and Trial Steering Committee: Professor Willie Hamilton – Independent chair ARCHIE programme steering committee Professor of Primary Care Diagnostics University of Exeter The Veysey Pool Building Salmon Pool Lane Exeter, EX2 4SG Tel: 01392 726097 Email: W.Hamilton@exeter.ac.uk Members: Dr Kay Wang – Chief Investigator of ARCHIE trial Tel: 01865 289312 Fax: 01865 289412 Email: kay.wang@phc.ox.ac.uk ~~Dr~~ Professor Anthony Harnden –ARCHIE Programme Lead Tel: 01865 289314 Fax: 01865 289412 Email: anthony.harnden@phc.ox.ac.uk Dr Calum Semple Tel: 0151 252 5440 Email: m.g.semple@liverpool.ac.uk Professor Judy Breuer – Independent member ARCHIE programme steering committee Professor of Virology University College London Division of Infection and Immunity Cruciform Building London, WC1E 6BT Tel: 020 3108 2130 Email: j.breuer@ucl.ac.uk ~~Dr~~ Professor Maureen Baker – Independent member ARCHIE programme steering committee Royal College of General Practitioners elected chair Email: mbaker@rcgp.org.uk Dr Theresa Clark – Independent PPI representative ARCHIE programme steering committee Email: theresaclark1234@aol.com

	Data and Safety Monitoring Committee Chair: ~~TBC~~ Dr Lorcan McGarvey MD FRCP Centre for Experimental Medicine School of Medicine, Dentistry and Biomedical Sciences Queen's University Belfast Telephone: 028 9097 6377 Email: l.mcgarvey@qub.ac.uk Mike Bradburn- Independent Statistician Member Senior Medical Statistician School of Health and Related Research, Clinical Trials Research Unit University of Sheffield, Sheffield, UK Email: m.bradburn@sheffield.ac.uk Surinder Birring- Independent Member Email: surinder.birring@nhs.net Nick Francis- Independent -Member Email: FrancisNA@cf.ac.uk

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2. SYNOPSIS

Trial Title	The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care (ARCHIE): a double-blind randomised placebo-controlled trial
Internal ref. no. (or short title)	KW/ARCHIE/0009
Clinical Phase	IV
Trial Design	Double-blind randomised placebo-controlled trial
Trial Participants	'At risk' children with influenza/influenza-like illness
Planned Sample Size	650
Treatment duration	5 days
Follow up duration	For the majority of participants, follow-up will be for 28 days from study entry, for the primary outcome of the trial. For participants whose parents/guardians give consent for additional follow-up throat swabs, follow-up will be for 12 months from study

	entry. (Date of study entry defined as date of randomisation).	
Planned Trial Period	October 2013 to ~~March~~ May ~~2017~~ 2019 inclusive	
	Objectives	Outcome Measures/Endpoints
Primary	To determine whether early treatment with co-amoxiclav reduces the likelihood of re-consultation due to clinical deterioration in 'at risk' children with influenza/influenza-like illness (ILI) within 28 days of study entry.	Proportion of children re-consulting due to clinical deterioration within 28 days of study entry.
Secondary	• To determine whether early treatment with co-amoxiclav reduces duration of fever in 'at risk' children with influenza/ILI. • To determine whether early treatment with co-amoxiclav reduces duration of symptoms in 'at risk' children with influenza/ILI. • To compare further intervention rates in 'at risk' children with influenza/ILI treated with co-amoxiclav versus placebo. • To compare adverse events in 'at risk' children with influenza/ILI treated with co-amoxiclav versus placebo.	• Duration of fever from time of study entry. • Duration of symptoms from time of study entry. • Proportion of children prescribed medication (*e.g.* antibiotics, steroids) and/or requiring further investigations (*e.g.* chest X-ray) within 28 days of study entry. • Proportion of children in whom adverse events are reported within 28 days of study entry. • Proportion of children who are hospitalised or die within 28 days of study entry.
Tertiary	• To develop and validate risk scores for influenza-related clinical deterioration and complications for use in children with influenza/ILI. • To explore the cost-effectiveness of different potential strategies for early antibiotic use in 'at risk' children with influenza/ILI. • To examine the impact on antibiotic resistance of early co-amoxiclav use in 'at risk'	• Health-related quality of life using the EQ-5D-Y and EQ-5D-Y proxy on days 1, 4, 7, 14 and 28. • Healthcare resource utilisation and parental/informal care costs within 28 days of study entry. • Minimum inhibitory concentrations (MICs) of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* in

	children with influenza/ILI. • To determine the impact on long-term respiratory bacterial carriage of early co-amoxiclav use in 'at risk' children with influenza/ILI.	relation to a representative range of antibiotics 3 months, 6 months and 12 months after study entry. • Proportion of ampicillin-resistant *Haemophilus influenzae* 3 months, 6 months and 12 months after study entry. • Prevalence of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* at 12 months after study entry.
Investigational Medicinal Product(s)	Co-amoxiclav 400/57	
Formulation, Dose, Route of Administration	**Formulation:** Amoxicillin 400 mg as trihydrate, clavulanic acid 57 mg as potassium salt)/5 mL liquid when reconstituted with water. **Dose:** Health care professionals will use their clinical judgement when advising on study medication doses in any children to whom it is felt that the standard British National Formulary (BNF) dosing recommendations should not apply.	

Child's age	Study medication dose
6 months to 23 months • Under 6 kg	Calculate dose according to BNF instructions for co-amoxiclav 400/57. Advise two doses daily for 5 days
• 6.0 – 7.9 kg	1 ml twice daily for 5 days
• 8.0 – 10.9 kg	1.5 ml twice daily for 5 days
• 11.0 – 12.9 kg	2 ml twice daily for 5 days
2 to 6 years	2.5 ml twice daily for 5 days
7 to 12 years	5 ml twice daily for 5 days

Route of administration: oral

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3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BNF~~BSAC~~	British National Formulary~~British Society of Antimicrobial Chemotherapy~~
BSAC	British Society of Antimicrobial Chemotherapy

CARIFS	Canadian Acute Respiratory Illness and Flu Scale
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trial
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials & Research Governance, University of Oxford
DMP	Data Management Plan
DSMC	Data and Safety Monitoring Committee
DVS	Data Verification Site
eGFR	Estimated glomerular filtration rate
EQ-5D	EuroQoL-5D
EQ-5D-Y	EuroQoL-5D Youth version
GCP	Good Clinical Practice
GP	General Practitioner
HIV	Human Immunodeficiency Virus
HRQL	Health-related quality of life
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ILI	Influenza-like illness
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimum inhibitory concentration (*i.e.* the lowest concentration of antimicrobial that will inhibit the visible growth of a micro-organism after overnight incubation)
MIC_{50}	Minimum inhibitory concentration 50 (*i.e.* the MIC value below which the MIC values of 50% of micro-organisms lie)
MIC_{90}	Minimum inhibitory concentration 90 (*i.e.* the MIC value below which the MIC values of 90% of micro-organisms lie)

ISF	Investigator Site File
NAI	Neuraminidase Inhibitor
NRES	National Research Ethics Service
PC-CTU	Primary Care – Clinical Trials Unit
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PSC	Programme Steering Committee
QALD	Quality-Adjusted Life-Days
QALY	Quality-Adjusted Life-Years
QP	Qualified Person
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDD	Study Data Document
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SQL	Structured Query Language
SSL	Secure Socket Layer
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSG	Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group

4. BACKGROUND AND RATIONALE

Research question

Does early treatment with co-amoxiclav reduce the likelihood of re-consultation due to clinical deterioration in 'at risk' children presenting with influenza/influenza-like illness (ILI) in primary/ambulatory care

Definition of 'at risk' children

'At risk' children are defined as children with underlying medical conditions or risk factors associated with an increased likelihood of developing influenza/ILI-related complications. Based on guidance from the UK Department of Health (DOH, 2006) and the US Advisory Committee on Immunization Practices (ACIP) (ACIP, 2010), 'at risk' groups include patients with chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes mellitus and immunosuppression. The definition of 'at risk' children which will be used in this study is explained in section 7.

Importance of the health problem to the NHS

Influenza and influenza-like illness (ILI) in children create a considerable burden on NHS resources each winter. In England, an average of 581 per 100,000 children under 4 years of age and 409 per 100,000 children aged 5 to 14 years visited their GP with influenza/ILI during each influenza season from 2002/3 to 2007/8 (Paget et al., 2010). The highest primary care consultation rates for ILI have often been found in children, both before (Mook et al., 2008, Desai et al., 2006) and since (HPA, 2011) the 2009 influenza pandemic.

Respiratory symptoms are the most commonly encountered symptoms in children who consult in a range of primary care settings, including general practices, out-of-hours centres and walk-in centres (Whitburn et al., 2011). Based on data from the Hospital Episode Statistics and Office of National Statistics, 490,000 GP consultations and 4200 hospitalisations due to seasonal influenza occur each year in children aged 14 years or younger (Pitman et al., 2007). This results in a cost to the NHS of approximately £6.7 million due to hospitalisations (based on a reference cost of £1606 per hospital inpatient stay (DOH, 2009)) and £18 million due to primary care consultations (Curtis, 2010). The overall NHS and wider socioeconomic burden is likely to be greater due to additional costs incurred in association with critical care admissions, Accident and Emergency Department attendances, clinical interventions (investigations and medications) and parental productivity losses (days off work and childcare costs).

Influenza/ILI is well recognised as a predisposing factor for secondary complications, including bacterial infections, which may result in children consulting a clinician more than once during the same illness episode due to clinical deterioration. Previous studies have demonstrated synergistic adverse effects on illness outcome if the respiratory tract is colonised with influenza and bacteria (McCullers, 2006, Wu et al., 2011, Okamoto et al., 2004, Tashiro et al., 1987). Based on data from the General Practice Research Database, influenza-related complications such as otitis media and pneumonia occur in 18% of at risk children versus 13% of otherwise healthy children within 30 days of initial presentation (Meier et al., 2000). These complications are likely to account for almost half of non-routine consultations due to clinical deterioration (Stott, 1979). Hospitalisation due to influenza/ILI is estimated to be five times more

likely in at risk children versus otherwise healthy children aged 0 to 4 years (214.4 versus 41.8 per 1000) and twelve times more likely in at risk children than otherwise healthy children aged 5 to 14 years (67.1 versus 5.6 per 1000) (Baguelin et al., 2010).

In recognition of the potential serious clinical and socioeconomic consequences of bacterial complications of influenza, the government stockpiles the antibiotic co-amoxiclav for use during influenza epidemics and pandemics. Out of all lower respiratory tract isolates of *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae* tested in laboratories in England during the most recent influenza season, 80% or more were susceptible to co-amoxiclav; no significant changes in susceptibility have been observed in recent years (HPA, 2011).

Need for research in this area

An effective, evidence-based policy on antibiotic use in at risk children during influenza season is needed to ensure that national antibiotic stockpiles are used in the most clinically appropriate and cost-effective way. There is a considerable burden created by bacterial infections in children, particularly at risk children, with influenza/ILI and a need for more effective strategies to reduce this burden than those currently available.

Although influenza vaccination is recommended in at risk children, reported uptake is variable among different groups. The Department of Health reported that during 2009-10, seasonal influenza vaccine uptake rates in children aged 6 months to 2 years varied between 13.4% in children with immunosuppression and 35.7% in children with diabetes on medication. In children aged 2 to 16 years, seasonal influenza vaccine uptake rates were between 22.6% in children with degenerative neurological disease and 61.7% in children with diabetes on medication (Begum and Pebody, 2010). A 2010-11 mid influenza season analysis conducted in the UK reported adjusted seasonal influenza vaccine effectiveness values of 34% (vaccinated season 2009/10 only), 46% (vaccinated 2010/11 season only) and 63% (vaccinated both seasons) in relation to 2009 influenza A/H1N1. Adjusted 2010/11 seasonal influenza vaccine effectiveness was 50% (95% confidence interval 17-70%) in relation to influenza A(H3) or B (Pebody et al., 2011).

A Cochrane review of published trials of neuraminidase inhibitors (NAIs) for the treatment and prevention of influenza in children before the 2009 pandemic (Wang et al., 2012) found that NAIs only conferred modest clinical benefit, reducing duration of symptoms in otherwise healthy children with influenza by about one day. None of the included trials were sufficiently powered to look at influenza-related pneumonia or hospitalisation. Furthermore, evidence of the role of NAIs in at risk children is currently weak. Only one trial involved children with asthma (Johnston et al., 2005) and found that oseltamivir did not reduce asthma exacerbations or improve peak flow. Oseltamivir is not licensed in children under the age of 1 year (FDA, 2006). Zanamivir is not recommended in individuals with underlying airways disease (such as asthma) due to risk of serious bronchospasm (MHRA, 2009).

Summary of current evidence

Influenza is a viral infection which circulates mainly during winter and is a well recognised risk factor for bacterial complications. 'At risk' children are more prone to becoming seriously unwell from influenza-

related complications than otherwise healthy children. Antiviral medications (neuraminidase inhibitors) confer limited clinical benefit, reducing duration of symptoms by about a day in otherwise healthy children. There are also insufficient published trial data to determine whether neuraminidase inhibitors reduce the incidence of influenza-related pneumonia or hospitalisations, particularly in 'at risk' children.

This double-blind randomised placebo-controlled trial will determine whether early treatment with the antibiotic co-amoxiclav reduces the likelihood of re-consultation due to clinical deterioration in at risk children who present with influenza/ILI in primary care. We will also examine the cost-effectiveness of early co-amoxiclav treatment as well as develop and validate prognostic risk scores to identify which children are likely to gain greatest clinical benefit.

'At risk' children who present in primary care with an influenza-like illness will be randomised to receive a five-day course of co-amoxiclav or placebo. Study medication will be initiated within 5 days of symptom onset because pneumonia and other bacterial infections can develop rapidly in 'at risk' children following influenza infection. A large observational study reported that 33% of children admitted to the Paediatric Intensive Care Unit with confirmed or probable pandemic influenza H1N1 had a clinical diagnosis of bacterial pneumonia or evidence of another bacterial infection within 72 hours of admission. Seventy percent of these children had 'at risk' underlying medical conditions and had mostly presented in the emergency department with a median influenza/ILI symptom duration of 3 days (interquartile range 1 to 5 days) (Randolph et al., 2011). Study medication doses will be calculated according to British National Formulary guidelines. Co-amoxiclav is a licensed medication whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10) (GlaxoSmithKline UK 2012).

Although there is a substantial evidence base underpinning recommendations that routine antibiotic treatment is not indicated for viral respiratory tract infections (RTIs) (Spurling et al., 2011, Petersen et al., 2007, NICE, 2008), there is also extensive preliminary evidence to suggest that early antibiotic use may be beneficial in preventing clinical deterioration and complications due to influenza. The results of a small randomised placebo-controlled trial suggest that early treatment with the antibiotic sultamicillin in children presenting with influenza/ILI during influenza season significantly reduces the incidence of pneumonia (Maeda et al., 1999). Published observational data have also previously demonstrated that duration of fever was significantly shorter in children with laboratory-confirmed influenza who had received antibiotics (mostly amoxicillin) at an early stage during their illness. This finding was not observed in children with any other type of viral infection (Harnden et al., 2007).

National government stockpiles of co-amoxiclav are held for use during influenza epidemics and pandemics. An evidence base to underpin clinically appropriate and cost-effective use of these stockpiles is needed. The broader range of antimicrobial coverage (because of the addition of clavulanic acid to amoxicillin), the twice daily dosing regimen and the importance of *Staphylococcus aureus* as a cause of severe bacterial pneumonia in influenza make this our preferred study antibiotic.

5. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	Outcome Measures/Endpoints
Primary Objective To determine whether early treatment with co-amoxiclav reduces the likelihood of re-consultation due to clinical deterioration in 'at risk' children with influenza/influenza-like illness (ILI) within 28 days of study entry.	**Primary Outcome Measures/Endpoints** The proportion of children re-consulting due to clinical deterioration within 28 days of study entry.*
Secondary Objectives • To determine whether early treatment with co-amoxiclav reduces duration of fever in 'at risk' children with influenza/ILI. • To determine whether early treatment with co-amoxiclav reduces duration of symptoms in 'at risk' children with influenza/ILI. • To compare further intervention rates in 'at risk' children with influenza/ILI treated with co-amoxiclav versus placebo. • To compare adverse events in 'at risk' children with influenza/ILI treated with co-amoxiclav versus placebo.	**Secondary Outcome Measures/Endpoints** • Duration of fever from time of study entry. • Duration of symptoms from time of study entry. • Proportion of children prescribed medication (e.g. antibiotics, steroids) and/or requiring further investigations (e.g. chest X-ray) within 28 days of study entry. • Proportion of children in whom adverse events are reported within 28 days of study entry. • Proportion of children who are hospitalised** or die within 28 days of study entry.
Tertiary Objectives • To develop and validate risk scores for influenza-related clinical deterioration and complications for use in children with influenza/ILI. • To explore the cost-effectiveness of different potential strategies for early antibiotic use in 'at risk' children with influenza/ILI. • To examine the impact on antibiotic resistance of early co-amoxiclav use in 'at risk' children with influenza/ILI. • To determine the impact on long-term respiratory bacterial carriage of early co-amoxiclav use in 'at risk' children with influenza/ILI.	**Tertiary Outcome Measures/Endpoints** • Health-related quality of life using the EQ-5D-Y and EQ-5D-Y proxy on days 1, 4, 7, 14 and 28. • Healthcare resource utilisation and parental/informal care costs within 28 days of study entry. • Minimum inhibitory concentrations (MICs) of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* in relation to a representative range of antibiotics 3 months, 6 months and 12 months after study entry. • Proportion of ampicillin-resistant *Haemophilus influenzae* 3 months, 6 months and 12 months after study entry.

	• Prevalence of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* at 12 months after study entry.

*Re-consultation is defined as any subsequent visit to a primary care or other equivalent ambulatory care setting within 28 days of entering the trial. Any community or hospital setting where 'at risk' children are seen on initial presentation with influenza/ILI will be considered suitable. Suitable settings may include, but are not limited to, general practices, out-of-hours primary care centres, Accident and Emergency departments, day assessment units and specialist clinics.

** Hospitalised is defined as admitted to a hospital ward or intensive care unit for at least one overnight stay.

Clinical deterioration is defined as any of: worsening symptoms, development of new symptoms or development of a complication requiring medication or hospitalisation after randomisation. This definition is based on that used by the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infection in Europe) consortium in relation to lower respiratory tract infections (Little et al., 2013).

Date of study entry is defined as the date of randomisation.

6. TRIAL DESIGN

6.1. Summary of Trial Design

This is a double-blind randomised placebo-controlled trial whose primary objective is to determine whether treatment with a 5-day course of co-amoxiclav early during an influenza/ILI episode in at risk children reduces the likelihood of re-consultation due to clinical deterioration.

'At risk' children aged 6 months to 12 years inclusive who present in primary care or other equivalent ambulatory care settings with influenza/ILI and meet our trial eligibility criteria will be invited to join the trial. For each child entering the trial a healthcare professional will complete a baseline assessment and obtain two swabs: a nasal swab for detection of influenza by Polymerase Chain Reaction (PCR) and a throat swab for bacterial culture and sensitivity.

Participants will be randomised to receive either co-amoxiclav 400/57 or placebo, which will be taken orally twice daily for 5 days. Parents/guardians of trial participants will be given a study diary in which to record doses of study medication given to the child, temperature, symptoms and adverse events. Parents/guardians will also be asked to record in their study diaries items relating to healthcare resource utilisation, parent or child burden. Children will be given a diary where they will have the opportunity to record medication taken and document how they are feeling each day.

Parents/guardians will be asked to complete a quality of life questionnaire, the EuroQoL EQ-5D-Y youth proxy instrument (Rabin and de Charro, 2001), on behalf of their children on days 1 (day of study entry),

4, 7, 14 and 28. To validate these responses, they will also complete disease-specific questions from the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) on days 1 and 7 (Jacobs et al., 2000). Children will also be offered the chance to complete the EuroQoL EQ-5D-Y instrument on days 1, 4, 7, 14 and 28 (Ravens-Sieberer et al., 2010, Stevens, 2011, Wille et al., 2010, Willems et al., 2009) .

An appropriately trained healthcare professional or member of the research team will contact the parents/guardians of trial participants one week and two weeks after study entry to record data on health service contacts, and adverse events, duration of fever, medication compliance, and to remind parents/guardians to complete their study diaries and questionnaires.

A healthcare professional or member of the research team will extract data from each child's medical record on consultations which occurred during the 12-month period before study entry, vaccinations, antibiotics prescribed during the 3-month period before study entry and investigations, medications prescribed, hospitalisations and consultations with clinicians in primary care or other equivalent ambulatory care settings during the 28-day period after study entry.

A healthcare professional will obtain follow-up throat swabs at 3, 6 and 12 months after study entry from those children whose parents/carers give consent for this. Data on antibiotic prescriptions during the 12-month period after study entry will be extracted from the medical notes of these children.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

'At risk' children presenting with influenza/ILI in primary care. For children to be eligible to take part in the trial, all inclusion criteria must be present and all exclusion criteria must be absent.

7.2. Inclusion Criteria

- Aged 6 months to 12 years inclusive.
- In 'at risk' category*.
- Presenting with influenza-like illness (i.e. cough and fever**) during influenza season.
- Presenting within 5 days of symptom onset.
- Permanently registered at a general practice in England UK.
- Parent /guardian able to complete study diary and questionnaires.

7.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Known contraindication to co-amoxiclav ***.
- Child given antibiotics for treatment of an acute infection within the last 72 hours.
- Child requires immediate antibiotics (clinician's judgement).
- Child requires immediate hospital admission for treatment of an influenza-related complication (clinician's judgement).

- Child has been observed on hospital ward or ambulatory care unit for longer than 24 hours. requires hospital admission
- Presence of any reason to prevent healthcare professional from obtaining high nasal swab.
- Child with known cystic fibrosis.
- Child previously entered into the ARCHIE study.
- Child has been involved in another medicinal trial within the last 90 days.

***'At risk' categories:**

The following 'at risk' categories are intended to guide clinicians in identifying which children are likely to be at greater risk of influenza-related clinical deterioration or complications. However, healthcare professionals should also use their own clinical judgement to identify 'at risk' children and may discuss children whom they think may be 'at risk' with a medically qualified member of the research team.

Respiratory

- Asthma requiring continuous or repeated use of controller therapy (e.g. inhaled steroids, leukotriene receptor antagonists, long-acting beta agonists, systemic steroids).
- Admitted to hospital with exacerbation of asthma within the last 12 months.
- Admitted to hospital with bronchiolitis or pneumonia within the last 12 months.
- Recurrent viral wheeze (3 or more episodes within the last 12 months).
- Bronchopulmonary dysplasia.

Cardiac

- Congenital heart disease being actively managed or monitored by cardiology team.
- Chronic heart failure being actively managed or monitored by cardiology team.

Neurological

- Chronic neurological or neuromuscular disorder which compromises respiratory function (e.g. cerebral palsy).

Renal

- Chronic kidney disease defined as either of the following:
- Impaired eGFR§ (estimated glomerular filtration rate) measurement within the last 12 months.
- Known hereditary or structural kidney abnormality with or without impairment in eGFR.
- Nephrotic syndrome.
- Kidney transplantation.

Liver§§

- Cirrhosis
- Biliary atresia
- Chronic hepatitis

Immunodeficiency

- Asplenia or splenic dysfunction.
- HIV infection.
- Undergoing chemotherapy leading to immunosuppression.
- Taking systemic steroids at a dose equivalent to prednisolone 20mg or more per day (any age) or >=1mg per kg per day (children under 20kg).

Other

- Diabetes mellitus (type 1 or type 2) or other metabolic condition.
- Genetic abnormality (e.g. Down's syndrome)
- Sickle cell disease

- Malignancy
- Prematurity (born before 37 weeks gestation) in children aged 6 to 23 months.

§Impaired eGFR is defined as an eGFR measurement of 59 ml/min/1.73m2 or less within the last 12 months before study entry. However, to enter the trial the following two conditions must also be satisfied:

1) eGFR >=30 ml/min/1.73m2 based on most recent measurement within the last 12 months;
2) no reason to suspect further deterioration in eGFR at time of study entry.

§§Children with mild or moderate liver disease may enter the trial. Children with severe liver disease may not enter the trial. Severe liver disease is defined as hepatic impairment associated with any of the following: jaundice, impaired coagulation/increased bleeding risk, bilirubin persistently greater than 50 micromol/litre (two measurements within last 12 months).

**Fever will be defined as any of the following: child-reported fever, parent-reported fever or temperature >37.8°C (axillary or tympanic temperature measurement).

***Contraindications to co-amoxiclav:**
Known hypersensitivity to beta-lactam antibiotics or clavulanic acid.
History of jaundice or hepatic impairment due to co-amoxiclav.
Severe liver disease§§
Known or suspected infectious mononucleosis.
Known lymphocytic leukaemia.
Known phenylketonuria.
eGFR less than 30 ml/min/1.73m2 (based on most recent measurement within the last 12 months).
Currently taking any medications known to interact with co-amoxiclav (e.g. probenecid, sulfasalazine, methotrexate, digoxin, oral anticoagulants) or increase the risk of adverse reactions to co-amoxiclav (allopurinol).

8. TRIAL PROCEDURES

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A summary table of study procedures is provided in appendix B.

8.1. Recruitment

~~7.4.~~

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We will recruit study participants from a range of health care settings where 'at risk' children from the community present with influenza-like illness. Recruiting sites will include general practices, walk-in centres and hospitals. Identification of participants at these sites may be supported by the use of participant identification centres. Baseline assessments and follow-up swabs may be conducted either at the recruiting site or in participants' homes.

Where possible, recruitment sites will be asked to perform database searches to identify children in 'at risk' groups before each recruitment season.

To raise awareness about the trial and of opportunities for participation, w. , We will provide a short information pre-season leaflet to inform the parents/guardians of these children about the study, which may be distributed by letterpost, or e-mail or at sites themselves to inform parents/guardians of 'at risk' children about the study. The leaflet will offer parents/guardians the opportunity to register their interest in the study. with the research team. The research team will inform the site of children whose parents/guardians register their interest in the study and ask them to put an alert on the medical notes of these children. The alert will indicate that these children and their parents/guardians have been informed about the study and registered an interest in taking part. Parents and guardians will also be able to register interest directly with the site.

Recruiting sites and participation identification centres will also be provided with other promotional study materials such as posters, short version participant information leaflets and interest cards.

The study may also be publicised via local news outlets, social media, charities working with relevant patient groups and the study website. Parents who express an interest in allowing their child to take part in the study will be able to contact the study team or look at the study website to find their nearest recruiting siterecruiter.

During each recruitment season, healthcare professionals from participating sites will screen children with influenza/ILI to determine whether they are eligible to take part in the trial based on our study inclusion and exclusion criteria. We will ask healthcare professionals to keep a study screening log of all at risk children who presented with influenza/ILI during the study period. The log will include details of whether or not these children met our other study eligibility criteria and whether or not consent was obtained from a parent or guardian. Where consent is not obtained, no identifiable details will be forwarded to the research team.

7.5.8.2. Informed Consent

An appropriately trained healthcare professional will gain written informed consent for each child to enter our trial from the child's parent or legal guardian. Our trial information leaflets and video will inform parents and children of the reasons for our trial and its potential risks and benefits. Parents and children will also be informed that they are free to leave the study at any time without giving a reason.

The majority of recruitment sites will be GP surgeries so the participant's clinician will be aware of their involvement in the study. However, when participants are recruited from a site other than their GP surgery, staff at the recruiting site will be requested to notify the child's general practice of the their participation in our study and to send them a copy of the completed consent form for the child's medical records.

The child's parent/guardian will consent to provide the child's name and NHS number as well as contact details for the child's parent/guardian and general practice. This information will enable the research team to arrange telephone follow-ups, reminders and obtain relevant data from the child's medical record (including primary outcome data). We will aim to gain consent from the parents/guardians of trial participants to obtain further throat swabs at three follow-up time points (3, 6 and 12 months after study entry). Healthcare professionals may will give parents/guardians who did not initially give consent for their child to have the optional follow-up swabs an additional opportunity to give verbal consent for these during the telephone follow-up. Parents/guardians who give verbal consent will be required to give written informed consent at the time of their child's 3-month follow-up throat swab.

7.6.8.3. Screening and Eligibility Assessment

Participants will be assessed against the eligibility criteria listed in section 7. If there is a delay between introduction of the study/initial eligibility assessment and consent/randomisation, then the recruiter must confirm all eligibility criteria are still met. This is documented on the baseline assessment.

A medically qualified individual or appropriately qualified nurse practitioner at the participating site will assess the child's eligibility for study inclusion. If informed consent, baseline assessment procedures and randomisation are to be completed by a different health care professional in the child's home, this should be done within 24 hours of eligibility being confirmed. If a health care professional is concerned that the child no longer meets study eligibility criteria at the time of the home visit, they should not recruit the child and seek medical advice.

7.7.8.4. Randomisation, blinding and code-breaking

Randomisation

The healthcare professional recruiting the child will use a web-based randomisation system. Randomisation will be stratified by region with minimisation for age (< 2 or ≥ 2 years old) and current seasonal influenza vaccination status (yes or no/don't know). The randomisation system will be implemented and managed by the PC-CTU. An emergency backup randomisation procedure will be available supported by the trial office.

Participants will be randomised with an allocation ratio of 1:1 treatment to placebo using Sortition (an online randomisation system developed and fully validated by the PC-CTU at the University of Oxford).

Blinding

Participants, their parents/guardians, healthcare professionals at recruiting sites and all research study staff will remain blinded to treatment allocation throughout the trial.

Codebreaking

A participant's treatment allocation will be unblinded in the event of a suspected unexpected serious adverse reaction (SUSAR). Procedures for unblinding of the randomisation code will be described in a Trial Specific SOP work instructions and include arrangements for an independent custodian of the randomisation codes to be appointed and access in working hours to individual codes from the independent custodian or their representative by the Chief Investigator or a designated named clinician.

Where there is a perceived need for unblinding, the clinician treating the patient should discuss the case with the Chief Investigator or a designated alternative study clinician. Access to randomisation codes will only be granted during working hours because immediate clinical management of a drug-related adverse event would not be affected by knowledge of the participant's treatment allocation. There is no antidote to co-amoxiclav (GlaxoSmithKline, 2008) and, if a drug-related adverse event occurs, the clinician is advised to discontinue the participant's study medication and treat the participant with a non beta-lactam antibiotic if antibiotic treatment is clinically indicated.

7.8.8.5. Baseline Assessments

Medical History

The healthcare professionals recruiting the child will collect data on date of birth, sex, co-morbidity, household smoking status, seasonal influenza vaccination status, duration of illness and duration of fever.

Concomitant Medication

The healthcare professionals recruiting the child will record data on antiviral medications and other medications taken during the current influenza/ILI episode.

Physical Examination

The healthcare professionals recruiting the child will measure and record the child's weight, heart rate, respiratory rate and temperature (axillary or tympanic).

Questionnaires

The healthcare professional will ensure the baseline questionnaires are completed: EQ-5D-Y proxy quality of life, EQ-5D-Y (if applicable) and CARIFS (disease specific).

Laboratory Tests

The healthcare professional will obtain two baseline swabs from all trial participants:

1. A ~~high~~ nasal swab for real-time Polymerase Chain Reaction (PCR) analysis to detect influenza and distinguish influenza A, B and A/H1N1 2009 pandemic subtypes. The swab will be placed in viral transport medium. Residual medium will be retained for potential future detection of other pathogens.

2. A throat swab for bacterial culture. The swab will have a broth medium to improve retrieval of the target organisms, which are *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Aliquots of the broth will be pipetted onto selective agar for each of the different organisms. A fourth plate, a selective agar for *Haemophilus influenzae* with ampicillin in the medium at 2mg/L will also be inoculated. Identification of target organisms will be performed in line with Public Health England Standards for Microbiological Investigation methods and susceptibility testing performed in accordance with the latest British Society of Antimicrobial Chemotherapy (BSAC) guidelines. The antimicrobials that will be used for susceptibility testing are shown below. Residual broth and isolates of the target organisms will then be put into long term storage for potential further molecular analysis of resistance and determination of phenotypic resistance. The broth will be frozen to either -70°C or -80°C, in effect snap frozen. Thus, there will be no preservation of intact cells.

Assessment of minimum inhibitory concentrations (MICs) will be performed according to the table below using the agar stipulated in BSAC guidelines.

Antimicrobial	**Method**	***S.aureus***	***S.pneumoniae***	***H.influenzae***
Penicillin	MIC	No	Yes	No
Amoxicillin	MIC	No	No	Yes
Co-amoxiclav	MIC	Yes	Yes	Yes
Cefoxitin	MIC	Yes	No	No

Cefotaxime	MIC	No	Yes	Yes
Moxifloxacin	MIC	Yes	Yes	Yes
Erythromycin	MIC	Yes	Yes	No
Nalidixic acid	Disc 30µg	No	No	Yes

Table footnote:
MIC = Minimum Inhibitory Concentration
S. aureus = *Staphylococcus aureus*
S. pneumoniae = *Streptococcus pneumoniae*
H. influenzae = *Haemophilus influenzae*

~~7.9.~~8.6. Subsequent Visits/Assessments

Parental diary

We will ask parents/carers to record the following information in their study diary:

1. Doses of study medication given to the child.

2. Axillary temperature daily at bedtime or before giving antipyretics (whichever occurs sooner) until the child's temperature has been below 37.5°C for 48 hours.

3. Symptoms daily until the child has recovered. These will be based on the symptom diary used by Little et al (Little et al., 2005).

4. Adverse events occurring within 28 days of study entry.

5. Items relating to parent or child burden as a result of the child's illness episode within 28 days of study entry, including absence from work, foregone leisure and productivity time (i.e absenteeism) and children's time off from school or day care.

Child diary

We will provide a diary for children which will offer them the opportunity to document their participation by recording the following information:

1. Taking their study medication.

2. How they are feeling each day.

Quality of life measures

We will ask all parents/guardians to complete the EuroQol EQ-5D-Y proxy version on behalf of their children (Rabin and de Charro, 2001) on days 1, 4, 7, 14 and 28. This will enable a clear evaluation of the change in children's health-related quality of life (HRQL) (utility) during the course of their illness. Parents/guardians will also be asked to complete disease-specific items from the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) (Jacobs et al., 2000) on days 1 and 7.

In addition to the EQ-5D-Y proxy version questionnaire, all children will be asked to complete the EQ-5D-Y on days 1, 4, 7, 14 and 28 (Ravens-Sieberer et al., 2010, Stevens, 2011, Wille et al., 2010, Willems et al., 2009).The EQ-5D-Y should be completed in addition to the EQ-5D-Y proxy version, to ensure that, where

feasible, we obtain both parental proxy valuations and childrens' own valuations. The EQ-5D-Y is adapted directly from the EQ-5D to calculate utility values for children (Wille et al., 2010). It features a 5-dimension descriptive system with three severity levels per dimension (no problems, some problems, lots of problems) and questions with age appropriate wording. Children will still be able to take part in the rest of the study if they are unable to or decide not to complete these EQ-5D-Y questionnaires.

Telephone follow-up and reminders

A healthcare professional or a member of the research team will arrange telephone follow-up calls after one week (between day 7 and day 10) and two weeks (between day 14 and day 17). T as well as text, e-mail or telephone reminders on days 4, 21 and 28 may also be agreed.

At the week 1 and week 2 telephone follow-ups, a healthcare professional/researcher will ask parents/guardians about health service contacts, adverse events, duration of fever, medication compliance, health service contacts and adverse events and remind them to complete their study diaries and questionnaires (parents/guardians: EQ-5D-Y proxy and CARIFS on day 7, EQ-5D-Y proxy on day 14; children: EQ-5D-Y on days 7 and 14). Adverse events will be reported to the PC-CTU. Text or e-mail reminders will may replace the week 1 and week 2 telephone follow-ups if these do not take place or cannot be scheduled.

The day 4 reminder will remind parents/guardians and children to complete their day 4 EQ-5D-Y proxy and EQ-5D-Y questionnaires respectively. The 21 day reminder will remind parents/guardians to return the week three diary. The day 28 reminder will remind parents/guardians and children to complete their day 28 EQ-5D-Y proxy and EQ-5D-Y questionnaires respectively.

Medical Notes

A healthcare professional or member of the research team will extract data from the child's medical notes on medical conditions, regular medications, vaccinations, consultations which occurred up to 12 months before study entry and antibiotics prescribed up to 3 months before study entry.

Data will also be extracted on re-consultations due to clinical deterioration from days 1 to 28 inclusive for our primary outcome measure. Data on items relating to healthcare resource utilisation, including medications, investigations, hospitalisations and consultations in primary care or equivalent ambulatory care settings (including details of dates and length of stay) will also be extracted. For children whose parents/guardians gave consent for them to have follow-up throat swabs, a researcher will collect data on antibiotics prescribed during the 12-month period after study entry or until the last follow-up throat swab was obtained.

Throat swabs

A healthcare professional or research nurse will obtain further throat swabs 3, 6 and 12 months after study entry from trial participants whose parents or guardians gave consent for this.

7.10.8.7. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to discontinue their study medication or withdraw from the study at any time. In addition, the investigator may discontinue a participant's study medication or withdraw a participant from the study at any time if the investigator considers it necessary (e.g. the participant

experiences an adverse drug reaction, the participant's parent or guardian withdraws consent, or the investigator considers that further participation in the study would not be appropriate due to the personal circumstances of the participant or the participant's parent or guardian).

Discontinuation of study medication

Clinicians will be advised to discontinue a participant's study medication if he/she experiences an adverse drug reaction related to the study medication. In addition, clinicians will be advised to prescribe an appropriate non beta-lactam antibiotic if antibiotic treatment is indicated. Parents/guardians of participants whose study medication is discontinued will still be required requested to complete their study diaries and questionnaires and will still receive telephone follow-up calls unless they choose to withdraw consent for these.

Withdrawal

Once a participant withdraws or is withdrawn from the study, no actions will be taken to obtain data other than to monitor adverse events (see section 10.3). Consent to proceed with reviewing the medical notes will be specifically confirmed for participants withdrawn from the study.

7.11.8.8. Definition of End of Trial

The end of the trial will be the date of the last medical notes review of the last trial participant.

8.9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

8.1.9.1. IMP Description

Medication:

Co-amoxiclav 400/57 (amoxicillin 400 mg as trihydrate, clavulanic acid 57 mg as potassium salt)/5 mL when reconstituted with water) or matching placebo. The co-amoxiclav 400/57 and matching placebo will be provided by Brown & Burk UK Ltd. The products will be manufactured by their parent company, Microlabs Ltd, at a dedicated penicillin site located in Bangalore India, approved by the UKMHRA. The placebo will be imported and QP released by Mawdsley Brooks & Co., Quest 22, Quest Park, Silk Road, Off Wheatley Hall Road, Doncaster DN2 4LT.

Dosing: Health care professionals will use their clinical judgement when advising on study medication doses in any children to whom it is felt that the standard British National Formulary (BNF) dosing recommendations should not apply

Child's age	Study medication dose
6 months to 23 months • Under 6kg	Calculate dose according to BNF instructions for co-amoxiclav 400/57. Advise two doses daily for 5 days
• 6.0 – 7.9 kg	1 ml twice daily for 5 days
• 8.0 – 10.9 kg	1.5 ml twice daily for 5 days

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• 11.0 – 12.9 kg	2 ml twice daily for 5 days
2 to 6 years	2.5 ml twice daily for 5 days
7 to 12 years	5 ml twice daily for 5 days

Administration:

Oral

Dosing Form:

Liquid

Packaging:

The study medication will be a powder for reconstitution in a 70ml HDPE opaque bottle with a child resistant cap. It will come in a pack which will also contain a patented syringe (Patented by Rovipharm) which can measure accurately up to 0.5ml.

Labelling:

The labelling of medication will conform to Annexe 13 (GMP) and Article 13.3 of Directive 2001/20/EC. A template label will be approved and provided by the clinical trial team to Mawdsley Brooks & Co. who will perform the labelling and the final Qualified Person (QP) release of the products.

Each medication pack label will be printed with a unique medication ID number to ensure co-amoxiclav 400/57 and placebo are indistinguishable and thus maintain allocation concealment (see 8.4 for randomisation process).

~~8.2.~~9.2. Storage of IMP

All coordinating centres and sites will store study medication in powder form at room temperature, in secure locations. Once the medication has been reconstituted the parent /guardian will be advised to store it in a refrigerator.

~~8.3.~~9.3. Compliance with Trial Treatment

Parents or guardians will be asked to record in their study diaries each dose of study medication given to the child. Compliance data will also be collected on either the 1 or 2 week follow-up CRF. Children whose study diaries indicate that they received 8 or more doses of study medication from days 1 to 6 inclusive will be considered to be compliant with study medication. All randomised trial participants will be included in the intention-to treat population.

~~8.4.~~9.4. Accountability of the Trial Treatment

Mawdsley Brooks & Co. will receive the IMP (marketed product) from Brown and Burk UK Ltd. and import the placebo from Microlabs Ltd. Mawdsley Brooks & Co. will perform the double blind labelling according to Annex 13 and provide final QP release. Mawdsley Brooks & Co. will release the study

medication to the PC-CTU. The PC-CTU will be responsible for the delivery of study medication to participating study region coordinator centres or participating study sites and all movements of study medication will be documented. It may be necessary to redistribute trial medication between participating sites. This will be documented on study logs.

~~8.5.~~9.5. Concomitant Medication

Trial participants will be advised to continue their usual regular medications while taking part in the trial. Healthcare professionals will record data at baseline on antiviral medications prescribed to participants during their current influenza/ILI episode. Trial participants will be advised to continue taking any antiviral medications prescribed before study entry.

Parents/guardians will be advised that they can give their children additional medications for their influenza/ILI episode while they are in the trial. They will be asked to record these additional medications in the study diary from days 1 to 28.

Since our trial will be double-blinded, clinicians will treat trial participants who re-consult in whatever way they feel is clinically appropriate. We will advise clinicians to prescribe an appropriate non beta-lactam antibiotic if they feel that antibiotic treatment is indicated in a trial participant who re-consults due to clinical deterioration within 28 days of trial entry.

We will also advise clinicians to prescribe any other medications to participants during the study period if they feel this to be clinically appropriate. A member of the research team will extract data from participants' medical notes on further antibiotics and other medications prescribed during the 28-day period after study entry.

~~8.6.~~9.6. Post-trial Treatment

Participants will only be asked to take their study medication for five days. After participants have finished taking their study medication, they will receive usual clinical care.

~~9.~~10. SAFETY REPORTING

Co-amoxiclav is a licensed medication whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10) (GlaxoSmithKline UK 2012). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment) an Adverse Event Report form will not be necessary.

Hepatitis and cholestatic jaundice associated with clavulanic acid are very rare (less than 1 in 10,000) and predominantly occur in patients who are over 60 years of age or treated with co-amoxiclav for 14 days or longer (MHRA 2009a). The maximum treatment course for children taking part in this study will be five days (ten doses) and children with known severe hepatic impairment will be excluded.

Unexpected adverse reactions to beta-lactam antibiotics will be highly unlikely amongst trial participants, as the vast majority of 'at risk' children will have previously received beta-lactams and/or co-amoxiclav to treat other infections. For non-serious adverse reactions to study medication, the Chief Investigator or a designated alternative study clinician will assess the urgency with which the participant's treatment allocation should be unblinded.

~~9.1.~~10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

~~9.2.~~10.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

~~9.3.~~10.3. Procedures for Recording Adverse Events

All AEs occurring in participants within 28 days of study entry observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF. However, Adverse Event Report forms will not be completed for common known side-effects of co-amoxiclav (mucocutaneous candidosis (thrush), diarrhoea, nausea and vomiting) (GlaxoSmithKline, 2012), provided they are non-serious and of mild to moderate severity (based on clinician’s assessment).

For AEs where Adverse Event Report forms will be completed, the following information will be recorded for each AE: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study medication as judged by a medically qualified investigator or the Sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant’s withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution or stabilisation occurs.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The relationship of AEs to the study medication will be assessed by a medically qualified individual.

~~9.4.~~10.4. Reporting Procedures for Serious Adverse Events

Appendix C contains a flowchart summarising the procedure for SAE reporting.

Healthcare professionals will report SAEs to the Primary Care Clinical Trials Unit at the University of Oxford (PC-CTU) within 24 hours of becoming aware of the event. A medically qualified individual will be responsible for assessing the relatedness of the SAE to study medication and reporting this to the PC-CTU. All SAEs will be reported using the PC-CTU SAE Report form which provides reporting directions. ~~The PC-CTU will maintain dedicated report lines with answerphone and fax facilities to allow reporting of SAEs.~~ The answerphone, emails and fax will be checked regularly during office hours.

The CI or their designated representative will be responsible for assessing the expectedness of SAEs reported as being related to study medication. Assessment of expectedness will be based on the Summary of Product Characteristics. Reporting procedures for Suspected Unexpected Serious Adverse Reactions (SUSARs) are described in section 10.6.

The CI or designated PI at each clinical site will supply any supplementary information as requested by the MHRA, REC or PC-CTU.

~~9.5.~~10.5. Expectedness

Expectedness will be determined according to the Summary of Product Characteristics.

~~9.6.~~10.6. SUSAR Reporting

All SUSARs will be reported by the CI or PC-CTU delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current study.

~~9.7.~~10.7. Safety Monitoring Committee

The trial Data and Safety Monitoring Committee will be responsible for reviewing SAEs after each recruitment season. The main aims of this review are as follows:

- To ensure the safety of each patient in the trial;
- To pick up any trends, such as increases in unexpected events, and take appropriate action;
- To seek additional advice or information from investigators where required;
- To evaluate the risk of the trial continuing and take appropriate action where necessary;
- To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment.

~~9.8.~~10.8. Development Safety Update Reports

In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial, or on request, a safety report to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

~~10.~~11. STATISTICS

~~10.1.~~11.1. Description of Statistical Methods

The principal comparisons will be performed on an intention-to-treat basis, as far as is practically possible, given any missing data. Specifically, the participants will be analysed in the groups to which they were allocated. Baseline characteristics will be summarised by treatment groups. The results from the trial will be presented as comparative summary statistics (difference in proportion or means) with 95% confidence intervals (CI). The analysis and reporting of results will follow the general principles of CONSORT 2010 statement.

The primary outcome (i.e. proportion of re-consultation rate) in the two groups will be compared using the Chi-squared test. Testing for a treatment effect after adjusting for minimisation factors, and other baseline covariates, will be conducted using multiple log-binomial regression models. Stability and assumptions of the regression model will be explored and alternative method will be used if any violation of assumptions occurred.

Analysis for secondary outcomes will be using similar methods described above. Continuous outcomes will be compared using t-test (Mann-whitney for non-normal data) and regression analysis, while binary outcomes will be compared using Chi-squared/Fisher's exact test and log-binomial regression.

Sensitivity analyses will be carried out to examine the robustness of the results with different assumptions about departures from randomisation policies, and handling of missing data.

A full detailed statistical analysis plan, including any pre-specified subgroup and sensitivity analyses, will be prepared before the final analysis by a statistician who is independent from the study.

Separate analysis plans will be prepared for other objectives, such as development and validation of risk scores, and health economics evaluation.

Development and validation of risk scores

We will develop risk scores in relation to two different clinical outcomes from our trial:
1) Re-consultation due to clinical deterioration.
2) Complications resulting in clinical intervention (i.e. prescription of medication or hospitalisation).

We aim to develop models for outcomes with at least 100 events. We will develop multivariable risk scores to group levels of risk for both types of clinical outcome using logistic regression. We will evaluate each model on variables defined in a separate statistical analysis plan for risk score development, which will be updated and finalised prior to data transfer for this project. Variables considered for the model will include age, type of co-morbidity, household smoking status, administration of the pneumococcal conjugate vaccine, administration of influenza vaccines from the current and previous influenza seasons, duration of illness at the time of study entry, heart rate, respiratory rate and influenza activity. We will also examine the arm of the trial to which children were randomised (co-amoxiclav or placebo) as a predictor. We will evaluate our risk scores using internal validation methods of bootstrap (Steyerberg, 2009, Harrell, 2001).

Cost analysis

Where possible, we will value items on healthcare resource utilisation using unit costs from published sources, including the most recent version of Unit Costs of Health and Social Care (Curtis, 2010) and NHS Reference Costs. We will estimate unit costs which are not available from secondary sources using the approach used in the most recent version of Unit Costs of Health and Social Care (Curtis, 2010). We will use the data collected from the medical notes as the primary source to inform the health care resource use. Where data from the medical notes is missing or unclear, details from the patient diaries will be used. Since quantification and costing of unpaid informal care is complex (Van den Berg et al., 2004), we will value these items using an opportunity cost method (i.e. at a 'would be' wage rate).

We will estimate total costs (Mihaylova et al., 2011) and costs relating to burden on primary care, secondary care and parental/informal care. We will extrapolate our analysis of resource use and costs to explore the potential cost impact of early co-amoxiclav use on a national scale. This will include service set-up costs, laboratory costs and potential impact on co-amoxiclav stockpiles.

Cost effectiveness analysis

We will estimate and report all the costs and consequences in a disaggregated format (cost-consequences analysis) as well as analysing and reporting the incremental cost and effectiveness in terms of cost per QALY of administering co-amoxiclav versus placebo in addition to standard care. QALYs or QALDs will be estimated and reported using data from the EQ-5D-Y questionnaire responses as our primary source. Where these are not available or incomplete, data from the EQ-5D-Y proxy version will be used. The validity of the responses to the EQ-5D-Y and proxy instruments will be compared with responses from the CARIFS.

We will explore uncertainty in the confidence to be placed on the economic analysis results through deterministic and probabilistic sensitivity analysis and presented by estimating cost-effectiveness acceptability curves. The sensitivity analyses will explore uncertainties in the trial data and analysis methods and the likely cost-effectiveness of treatment in periods of varying influenza activity.

We will also compare the cost-effectiveness of early co-amoxiclav treatment for all at risk children with ILI versus at risk children with laboratory-confirmed influenza only. We will also investigate the cost-effectiveness of early co-amoxiclav in at risk children based on their baseline risk of re-consultation due to clinical deterioration or complications resulting in clinical intervention.

Analysis of follow-up throat swabs

We will summarise baseline data on participant age, sex, co-morbidity and antibiotic prescriptions during the 3-month period before study entry and the 12-month period after study entry (i.e. from study entry until the 12-month follow-up throat swab has been obtained). To assess for any potential sampling bias, we will compare baseline characteristics of this subsample with those of all trial participants.

We will determine the number of colony forming units per ml for each of the target organisms at each time point of the study. The minimum inhibitory concentration of each target organism to the antimicrobial panel tested will be expressed in terms of the MIC50 and MIC90, and this will be plotted at each time point of the study when follow-up throat swabs are obtained.

We will apply a log transformation to MIC measurements and summarise these data using geometric means and 95% confidence intervals. We will fit a curve of MIC over time and calculate the area under the curve for species isolated from each child. We will use repeated measures analysis to compare the difference in MIC over time between the antibiotic and placebo groups.

We will determine the proportion of ampicillin-resistant *Haemophilus influenzae* at each time point by dividing the number of colonies on ampicillin-containing plates by the number of colonies on plates without ampicillin (Malhotra-Kumar et al., 2007).

We will compare the group prevalence of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* at 12 months among children in the co-amoxiclav and placebo arms. Data on swabs at 3 and 6 months will help impute information on children without a 12 month swab.

~~10.2.~~11.2. The Number of Participants

We will aim to recruit 650 children into the trial. This will include a loss to follow-up rate of 25%, giving an effective sample size of 484 children (242 children in each arm of the trial) (see appendix A).

Although we will be randomising individual patients, our effective sample size includes an inflation factor of 1.041, as intra-practice clustering may occur due to differences in physician care and prescribing rates. We estimate that our average cluster size will be 2 patients based on a recruitment rate of 65 patients per region per winter and an average of 2 clinicians randomising patients at each recruiting site. Based on a conservative intra cluster correlation estimate of 0.03 (Adams et al., 2004) and a coefficient of variation value of 0.6 (based on the value observed in the DD trial) (Woodcock et al., 1999), we estimate our inflation factor to be 1.041 (Eldridge et al., 2006).

Based on recent influenza surveillance data, we estimate that around 50% of children with clinical influenza will have laboratory-confirmed influenza (McLean et al., 2009, Michiels et al., 2011). We therefore estimate that 326 trial participants (163 in each arm) will have laboratory-confirmed influenza. Allowing for 20% loss to follow-up, we estimate that we will obtain data from 260 children (130 in each arm) for our planned exploratory subgroup analysis in children with laboratory-confirmed influenza.

~~10.3.~~11.3. The Level of Statistical Significance

A large population-based study using the UK General Practice Research Database found that true complications occurred in 17.6% of at risk children aged 1 to 14 years within 30 days of being clinically diagnosed with influenza/ILI (Meier et al., 2000). Assuming that true complications account for 44% of re-consultations due to clinical deterioration (Stott, 1979), we estimate that 40% (17.6%/44 x 100) of at risk children with clinical influenza will re-consult with clinical deterioration within 30 days of initial presentation.

A sample size of 484 children (242 in each arm) will allow us to detect a reduction in re-consultation due to clinical deterioration from 40% to 26% with 90% power and 5% alpha error. We believe that this treatment effect estimate (a 35% relative risk reduction) is conservative, given that a previous randomised controlled trial found that the rate of pneumonia in otherwise healthy children with clinical influenza was one-seventh of that in children who received the antibiotic sultamicillin versus placebo (16.3% versus 2.4%, an 85% relative risk reduction) (Maeda et al., 1999).

10.4.11.4. Criteria for the Termination of the Trial

The DSMC will review SAEs after each recruitment season and discuss these with the Trial Steering Committee (TSC). The DSMC, TSC or Sponsor may advise on whether the trial should be terminated.

10.5.11.5. Procedure for Accounting for Missing, Unused, and Spurious Data.

We will conduct an intention-to treat analysis and use multiple imputation methods for missing data.

10.6.11.6. Inclusion in Analysis

We will perform an intention to treat analysis including all randomised participants.

10.7.11.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

We do not anticipate any deviation from the statistical plan outlined above. However, provision for alternative methods and changes to analyses will be included in the Statistical Analysis plan as specified in the PC-CTU's SOP "Statistical Analysis Plan".

11.12. DATA MANAGEMENT

11.1.12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. Source documents will be comprised of the following:

- Case report forms (CRF) for baseline assessment, follow-up and study discontinuation (completed by researchers in consultation with participant or their healthcare professional)
- Medical records (from which medical history and previous and concurrent medication may be summarised into the CRF or entered directly into OpenClinica)
- Laboratory results
- Diaries (hard copies completed by parents/guardians/participants and electronic csv downloads of parent/guardian/participant completed PDFs).
- Correspondence (provided by participants, their healthcare professional or researcher).

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, assent and baseline contact information page, the participant will be referred to by the trial participant number/code, not by name.

11.2.12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.3.12.3. Data Recording and Record Keeping

Study data will be entered, or transferred, into OpenClinica (currently version 3.1.3.1). Participants will only be identified by a study-specific participant number and/or code in the OpenClinica database. Documents containing participant identifiable information will be stored separately from other study documents and saved within a securely hosted database separate from OpenClinica.

OpenClinica is a software package designed to capture, manage and store clinical trial data. Its usage enables compliance with Good Clinical Practice (GCP) and regulatory guidelines by offering differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, de-identification of protected health information and comprehensive auditing to record and monitor access and data changes.

All Data Management functions will be performed in accordance with PC-CTU DM SOPs, summarised by SOP DM1 "Data Management". A Data Management Plan (DMP) is in place for all PC-CTU hosted trials, outlining in detail the study specific procedures to ensure that high quality data is produced for statistical analysis. The DMP is reviewed and signed by all applicable parties, including the Trial Manager and the Trial Statistician, prior to the first patient being enrolled.

Clinical trial data will be collected by the PC-CTU in paper format, direct data capture, and also direct upload of trial data from external data sources (laboratory test results and csv downloads of participant completed PDFs). The final repository for all trial data will be OpenClinica.

All Study Data Documents (SDDs) in paper format are date stamped upon receipt and tracked within a trial management database. A full pre-entry review ensures that all pages have been received, subject identifiers are consistent and obvious errors/missing data are appropriately addressed prior to entry. All paper SDDs are double entered by two independent data entry staff into the clinical database.

Data validation for all data entered into the clinical database is achieved by programming study specific checks at point of entry, or by execution of SQL based queries. The Clinical Data Manager will review all discrepancies and generated output. If clarification from a research site is required, the query is added to a Data Verification Site (DVS) Report, and subsequently issued. The Clinical Data Manager oversees the tracking of DVS reports until they are resolved, and applies any updates to the clinical database.

Prior to database lock, dataset review is performed by the Clinical Data Manager and the Trial Statistician. All critical data items are 100% checked against original SDDs (and subsequent updates) to ensure accuracy, and an error rate is established across all fields to ensure a consistently accurate dataset.

At the conclusion of the trial and after the database has been locked, all essential documents will be archived until 3 years after the youngest participant reaches 18 years old and will follow PC-CTU's SOP TM24 "Archiving". The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

~~12.~~13. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. The PC-CTU has in place procedures for assessing risk management for adopted trials which will outline the monitoring required.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Healthcare professionals participating in our study will be asked to submit proof that they have completed GCP training, or be required to undertake GCP training (e.g. register for the online GCP course provided by the University of Oxford Clinical Trials and Research Governance (CTRG) team).

The Trial Management Group (TMG) will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the trial's day to day management (e.g. the CI, trial manager, statistician, data manager) and will meet regularly, at least on a monthly basis.

As the trial is the central workpackage in a wider programme of research, the Programme Steering Committee (PSC) will function as the Trial Steering Committee. The PSC will be convened to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The PSC will consist of at least 5 members including the Chief Investigator, a co-investigator and an independent member.

An independent Data and Safety Monitoring Committee (DSMC) will review the accruing trial data after each winter during the trial recruitment period and assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The DSMC will consist of an independent statistician and at least 2 independent members.

~~13.~~14. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree :

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed and, if appropriate, the Sponsor will report it to the REC, Regulatory Authority and the NHS host organisation within seven calendar days.

~~14.~~15. ETHICAL AND REGULATORY CONSIDERATIONS

~~14.1.~~15.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

~~14.2.~~15.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

~~14.3.~~15.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

~~14.4.~~15.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

~~14.5.~~15.5. Participant Confidentiality

The trial staff will ensure that the participants' confidentiality is maintained. Other than on the contact information sheet, consent form and, if applicable, assent form, participants will be identified only by a participant ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

~~14.6.~~15.6. Expenses and Benefits

We do not anticipate the need for reimbursement of any expenses. However, if there should be any, they will be processed according to the standard University guidelines.

~~14.7.~~15.7. Other Ethical Considerations

The following issues require consideration:

- Co-amoxiclav 400/57 is licensed for the treatment of a wide range of established infections in children, including chest, ear, throat and sinus infections. However, this trial will assess the effectiveness of co-amoxiclav in reducing the likelihood of clinical deterioration in children with influenza-like illness who may have subclinical or early bacterial infections.
- The trial design involves a placebo.
- The trial subjects are children.

~~15.~~16. FINANCE AND INSURANCE

~~15.1.~~16.1. Funding

The trial is funded by a National Institute for Health Research Programme Grant for Applied Research: RP-PG-1210-12012.

~~15.2.~~16.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered: WD1200463). NHS indemnity operates in respect of the clinical treatment which is provided.

~~16.~~17. PUBLICATION POLICY

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by an NIHR Programme Grant for Applied Research RP-PG-1210-12012. The publication policy for this Programme Grant will state the lead author(s) and co-authors for each manuscript. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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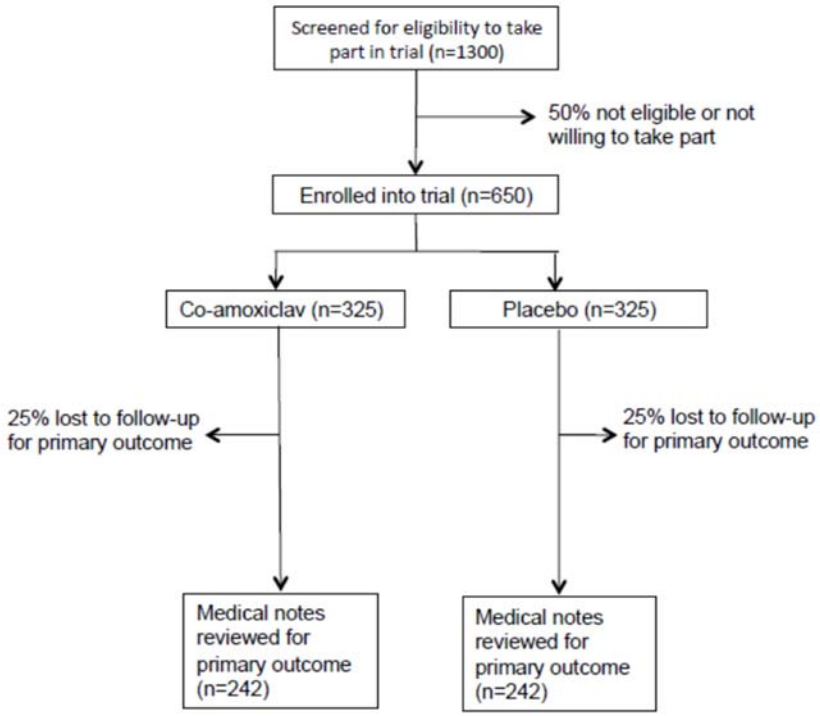
~~18.~~19. APPENDIX A: TRIAL FLOW CHART

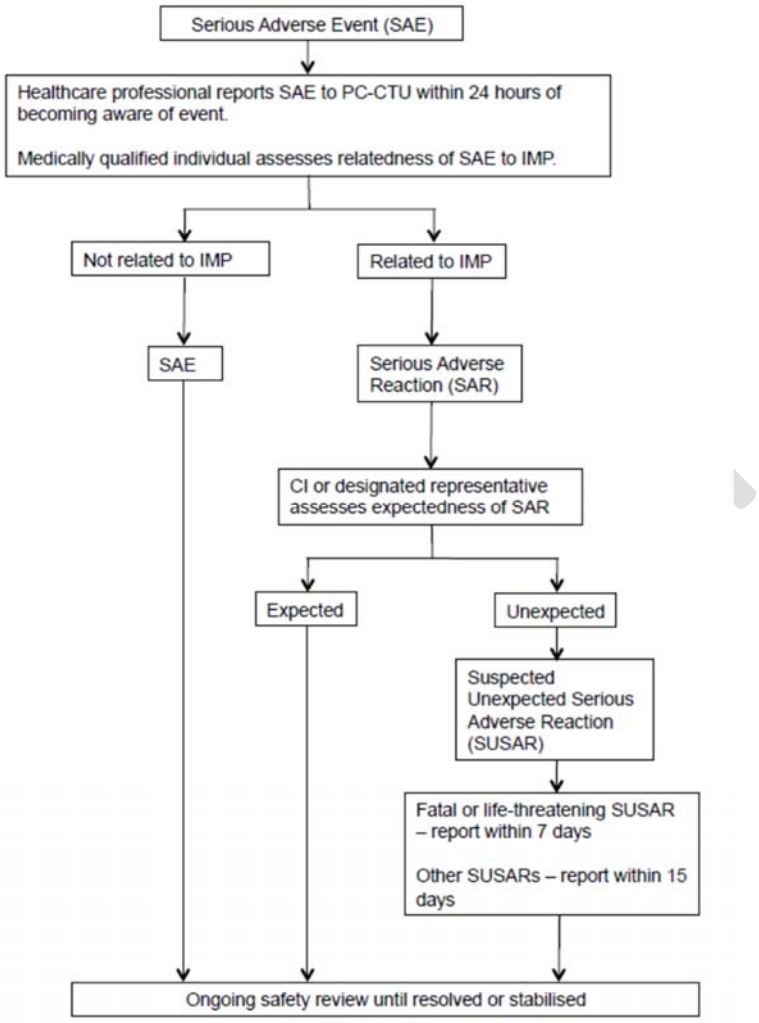


~~19.~~20. APPENDIX B: SCHEDULE OF PROCEDURES

Procedures	Enrolment		Post allocation (trial)			Follow-up swabs			Close out
	V1	V2	Diary	T1	T2	S1	S2	S3	NR
Eligibility assessment	x								
Informed consent +/- assent		x							
Baseline assessment		x							
Nasal swab		x							
Throat swab		x				(x)	(x)	(x)	
Randomisation		x							
Dispensing of study drug		x							
Allocation of study diary and pack		x							
Adverse events assessment				x	x				
Medical notes review									x
Assessments									
Age		x							
Sex		x							
Co-morbidity		x							x
Household smoking status		x							
Vaccination status		x							x
Antivirals/other medications		x							x
Regular medications									x
Heart rate		x							
Respiratory rate		x							
Baseline annual consultation rate									x
Re-consultations due to clinical deterioration									x
Duration of fever		x	x	x	x				
Duration of symptoms		x	x	x	x				
Further medications and/or further investigations									x
Adverse events				x	x				x
Hospitalisations/death				x	x				x
EQ-5D-Y proxy/EQ-5D-Y/CARIFS		x	x						

V1 = screening and eligibility assessment (face to face visit); V2 = enrolment (face to face visit); T1 = day 7 telephone follow-up; T2 = day 14 telephone follow-up; S1 = 3 month follow-up throat swab; S2 = 6 month follow-up throat swab; S3 = 12 month follow-up throat swab; NR = notes review

~~20.~~21. APPENDIX C: SAE REPORTING FLOW CHART



21.22. APPENDIX D: AMENDMENT HISTORY

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2		Tricia Carver	1. Definition of suitable recruitment sites: 'primary care' has been replaced with 'primary care and other equivalent ambulatory care settings'. Examples of potentially suitable recruitment sites are given in Section 5. 2. Section 9.4. Accountability of the Trial Treatment has been edited to reflect the responsibilities of Mawdsley Brooks & Co. 3. PSC to serve as TSC. 4. Department name updated to include "Nuffield" prefix.
2	2		Tricia Carver	1.Addition of new sites
3	2		Tricia Carver	1. Addition of new sites
4	2		Tricia Carver	1. Addition of new sites
5	2		Tricia Carver	1. Addition of new sites
6	2		Tricia Carver	1. Removal of temp restrictions from IMP label, dossier updated to reflect change 2. Reduction of placebo order
7	2		Tricia Carver	1. Cover letters to accompany mail out and text messages
8	2		Tricia Carver	1.Addition of new sites 2. Change of site PI's
9	2		Tricia Carver	1. Addition of primary care regions 2. Change of Site PI's
10	2		Tricia Carver	1. Press Release 2. Minor Notifications
11	2		Tricia Carver	1. Addition of new sites
12	2		Tricia Carver	1. Promotional materials 2. Notification of CRF updates
13	2		Tricia Carver	1. New sites
14	2		Tricia Carver	1. New IMP Dossier extending IMP shelf life
15	2		Tricia Carver	1. Addition of new sites 2. Change of Site PI's
16	2		Tricia Carver	1. Addition of PICS

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17	3		Tricia Carver & Sharon Tonner	1. Addition of investigator and updating of contact details 2. Clarified dosing regime based on BNF guidelines 3. Clarified date collected during telephone follow up calls including compliance data 4. Addition of vaccination data collection in trial design summary as previously omitted in error 5. Modified eligibility criteria to: a. Remove requirement that children should be registered at a GP surgery in England. Replaced this with exclusion criterion: "Presence of any known reason to prevent medical notes from being accessed during the 12-month period after study entry (e.g. child is permanent resident outside UK)." b. Clarify that exclusion criterion relating to antibiotic use within the last 72 hours refers specifically to use of antibiotics for treatment of acute infection. c. Clarify exclusion criteria relating to hospitalisation. 6. Addition of hospitalization with pneumonia to at risk category 7. Clarified recruitment and screening processes 8. Removal of term 'high' in reference to nasal swabs to better reflect actual procedure 9. Addition of availability of emergency randomization procedures 10. Changed reference to trial SOP's to working instructions to reflect PC CTU internal policy 11.Clarified SAE reporting procedures

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				12. Clarified planned trial period extentsion

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