ARCHIE

The early use of Antibiotics in 'at Risk' CHildren with InfluEnza

INVESTIGATOR SITE FILE

UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
Primary Care Clinical Trials Unit

Summary of steps to follow

1. Eligibility Assessment – Complete the eligibility assessment form online.

2. Baseline Assessment
- Complete baseline assessment form online.

- Ask parent/guardian to complete contact information and questionnaires.

- Take high nasal and throat swabs**.**

- Assign study medication using Sortition (web-based randomisation system).

- Issue and explain study pack (including study diaries and thermometer).

- Arrange text/email reminders and follow-up telephone calls.

- Post completed consent +/-assent forms and questionnaires in the pre-paid envelope.

3. Week 1 Follow-up (telephone)
- Complete Week 1 Follow-up form online.
- Report adverse events.

4. Week 2 Follow-up (telephone)
- Complete Week 2 Follow-up form
- Report adverse events.

5. Medical Notes Review

For participants whose parents/guardians give consent for follow-up throat swabs:

6. 3 month follow-up - Collect and post throat swab sample

7. 6 month follow-up - Collect and post throat swab sample

8. 12 month follow-up - Collect and post throat swab sample.

9. Additional Medical Notes Review

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Summary flow sheet 23Jun14 v0.3

Study Information Contact Page

Study 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)	
Protocol number: ARCHIE001	**ISRCTN:** ISRCTN70714783
REC number: 13/NW/0621	**R&D ref:** 121769
EudraCT number: 2013-002822-21	**CTA:** 21584/0321/001-0001

Start date: 1 October 2014 *(recruitment)*	**Projected end date:** 31 March 2016 *(recruitment)*

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FILENOTE LOG

File note number	Section	Title
01	8.1	**Not present: Subject ID forms**
02	8.4	**Not present: Screening records**
03	10.9	**Not present: Local pharmacy agreement**
04	11	**Not present: Equipment records**
05	1.2	**Informed Consent Form recording of version and date of PIS given and/or video viewed**

Primary Care Clinical Trials Unit

ARCHIE

INVESTIGATOR SITE FILE CONTENTS

Notes

For CTIMPs, where specific documents are deliberately absent, a file note should be included to record the justification for the absence.

If a listed document is stored elsewhere, a file note should be included to record its location.

Key: (E) indicates an essential document which must be officially archived to show regulatory compliance for CTIMPs. The study team will advise on archive location at the end of the study.

Study Flowchart	
Study Information and Contact Page	
File note Log	
Section 1	**Externally Approved Documents** *(keep superseded below current)* **1.1** Protocol, version controlled, signed & dated by CI **1.2** Informed Consent Form (ICF), version controlled **1.3** Patient Information Sheet(s) (PIS), version controlled **1.4** Patient recruitment literature/advertisements, version controlled, on local headed paper *if applicable* **1.5** Any letter/information for a participant's GP or Consultant **1.6** Examples of any other written information provided to the participants
Section 2	**Internal Trial Documents** *(keep superseded below current)* **2.1** Copies of blank CRFs, questionnaires and diaries, version controlled **2.2** CRF correction procedure **2.3** Working Instructions **2.4** Training material, e.g. presentations from training days **2.5** NOT APPLICABLE: Supplies re-order form template
Section 3	**Sponsorship, Funding and Agreements** **3.1** Sponsorship letter **3.2** Indemnity arrangements **3.3** Site contract / agreement **3.4** Service Support Cost information
Section 4	**Research Ethics Committee (REC)** REC favourable opinion letter, with approved documents and committee composition listed
Section 5	**Research and Development (R&D) Approval** **5.1** Global R&D approval letter **5.2** Local R&D approval letter
Section 6	**Competent/Regulatory Authority (e.g. MHRA for UK)** CTA acceptance letter
Section 7	**Amendments** *File approval letters here. Approved versions of new documents should be filed in Section A1.* Approval of substantial amendment letters (Sponsor, REC, MHRA, Global R&D and Local R&D) or acknowledgement of minor amendment letters

Section 8	**Patient Recruitment** *For archiving only – all identifiable information must be kept in accordance with PC-CTU SOPs* **8.1** *NOT APPLICABLE (filenote 01):* **(E)** Subject ID forms **8.2** **(E)** Original copies of completed Informed Consent Forms **8.3** **(E)** Completed CRFs/questionnaires (signed and dated) **8.4** *NOT APPLICABLE (filenote 02):* **(E)** Patient screening and recruitment records (or mail-out equivalents)
Section 9	**Personnel** **9.1** **(E)** Delegation log and signature form **9.2** **(E)** Signed and dated original CVs **9.3** **(E)** Evidence of training in GCP, e.g. certificate **9.4** **(E)** Evidence of training in trial training [protocol, PC-CTU SOPs, pharmacovigilence] e.g. signature confirmation of having read protocol
Section 10	**Investigational Medicinal Product (IMP) information / Pharmacy** **10.1** Investigator's Brochure (IB) and/or Summary of Product Characteristics (SmPC) **10.2** Safety alert updates **10.3** Instructions for handling trial medication and trial related materials (randomisation, supply, receipt, re-supply, return/destruction, code breaking) **10.4** Template accountability forms / inventory forms (Pharmacy) / dispensing logs / temperature logs **10.5** **(E)** Completed accountability documents (supply, shipping records etc) **10.6** Certification of IMP analysis and placebo if relevant **10.7** **(E)** Documentation of IMP destruction **10.8** Agreement with Pharmaceutical Company / IMP supplier **10.9** *NOT APPLICABLE (filenote 03):* **(E) Local** pharmacy agreements **10.10** Superseded IBs and/or SmPCs
Section 11	**Equipment** *NOT APPLICABLE (filenote 04)*
Section 12	**Monitoring and Audit** **12.1.** **(E)** Pre-trial/trial initiation reports **12.2** **(E)** Monitoring log **12.3** **(E)** Monitoring reports (monitoring visits/remote checks) **12.4** **(E)** Monitoring correspondence (including phone, follow-up letters etc) **12.5** **(E)** Site closure report
Section 13	**General correspondence** **(E)** Records of all significant telephone conversations and emails relating to the study
Section 14	**Safety** **14.1** Unblinding procedure for blinded trials **14.2** **(E)** Copies of broken blinds (at the end of the trial) **14.3** Template AE/SAE/SUSAR report forms **14.4** Reporting arrangements for SAE/SUSARs (if not in protocol) **14.5** **(E)** Copies of completed SAE/SUSAR forms **14.6** **(E)** SAE/SUSAR related correspondence

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 February 2014 v2

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RP-PG-1210-12012

Chief Investigator Signature: 10/3/2014

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

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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 2017 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	• 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

<table>
<tr><td></td><td>versus placebo.
• To compare adverse events in ‘at risk’ children with influenza/ILI treated with co-amoxiclav versus placebo.</td><td>study entry.
• Proportion of children who are hospitalised or die within 28 days of study entry.</td></tr>
<tr><td>Tertiary</td><td>• 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.</td><td>• 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.</td></tr>
<tr><td>Investigational Medicinal Product(s)</td><td colspan="2">Co-amoxiclav 400/57</td></tr>
<tr><td>Formulation, Dose, Route of Administration</td><td colspan="2">Formulation: Amoxicillin 400 mg as trihydrate, clavulanic acid 57 mg as potassium salt)/5 mL liquid when reconstituted with water.

Dose:
<table>
<tr><th>Child’s age</th><th>Study medication dose</th></tr>
<tr><td>6 months to 23 months
• 6.0 – 7.9 kg
• 8.0 – 10.9 kg
• 11.0 – 12.9 kg</td><td>
1 ml twice daily for 5 days
1.5 ml twice daily for 5 days
2 ml twice daily for 5 days</td></tr>
<tr><td>2 to 6 years</td><td>2.5 ml twice daily for 5 days</td></tr>
<tr><td>7 to 12 years</td><td>5 ml twice daily for 5 days</td></tr>
</table></td></tr>
</table>

	Route of administration: oral

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
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.	**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*,

• 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.	*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 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, 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.
- 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 within the last 72 hours.
- Child requires immediate antibiotics or hospital admission (clinician's judgement).
- 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 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

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

8.1. Recruitment

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, we will provide a short pre-season leaflet to inform the parents/guardians of these children about the study by letter or e-mail before each recruitment season. 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 will be provided with promotional study materials such as posters, short version participant information leaflets and interest cards to display and/or hand out, allowing the patients an opportunity to find out more about the study and consider participation.

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.

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 the 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 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.

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.

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.

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 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.

8.5. Baseline Assessments

Medical History

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

Physical Examination

The healthcare professional 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*

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^{o}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) as well as text, e-mail or telephone reminders on days 4, 21 and 28.

At the week 1 and week 2 telephone follow-ups, a healthcare professional/researcher will ask parents/guardians about 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 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.

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 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.

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.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

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:

Child's age	**Study medication dose**
6 months to 23 months • 6.0 – 7.9 kg • 8.0 – 10.9 kg • 11.0 – 12.9 kg	 1 ml twice daily for 5 days 1.5 ml twice daily for 5 days 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).

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.

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. 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.

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.

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.

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.

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.

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.

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.

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.

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. The PC-CTU will maintain dedicated report lines with answerphone and fax facilities to allow reporting of SAEs. The answerphone 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.

10.5. Expectedness

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

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.

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.

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.

11. STATISTICS

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.

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.

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).

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.

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.

11.6. Inclusion in Analysis

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

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".

12. DATA MANAGEMENT

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.

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.

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.

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.

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.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

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

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.

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.

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.

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.

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.

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.

16. FINANCE AND INSURANCE

16.1. Funding

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

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.

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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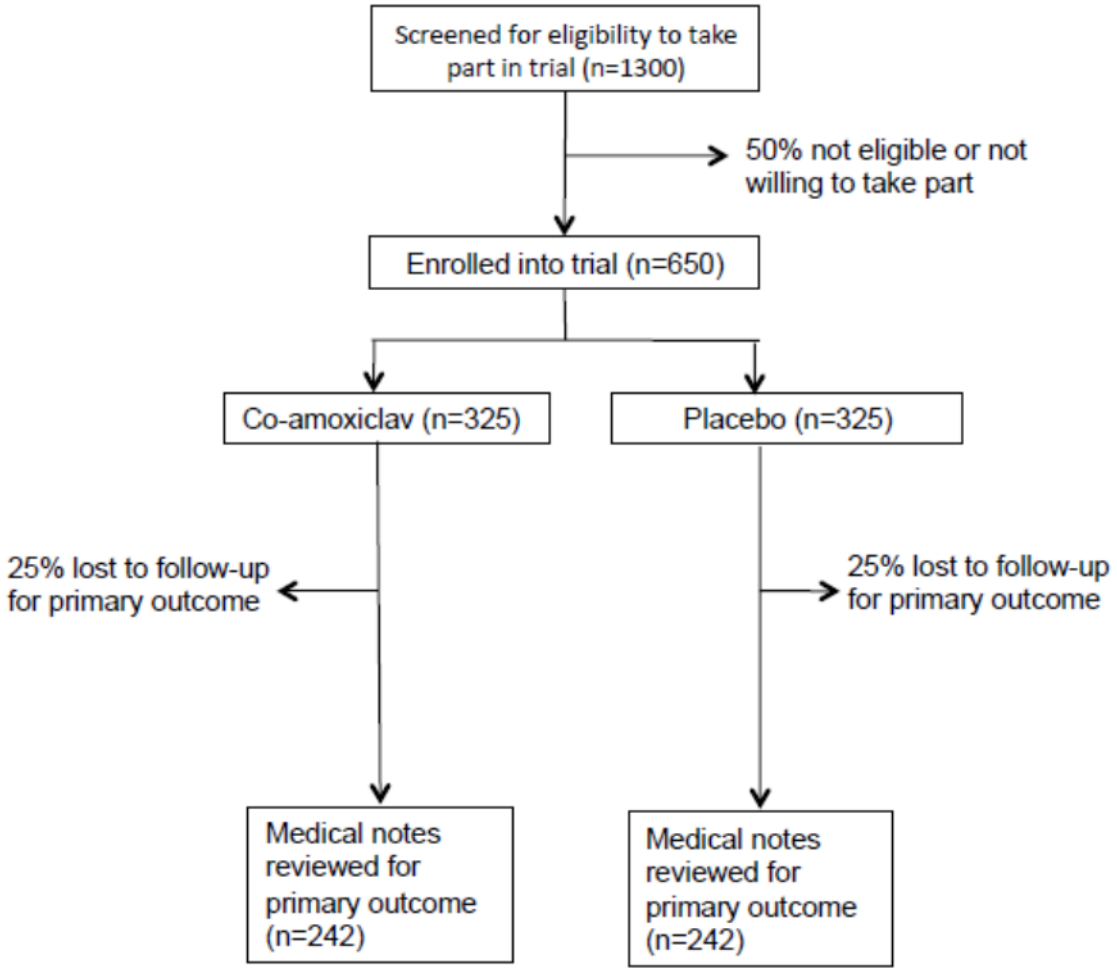
19. APPENDIX A: TRIAL FLOW CHART

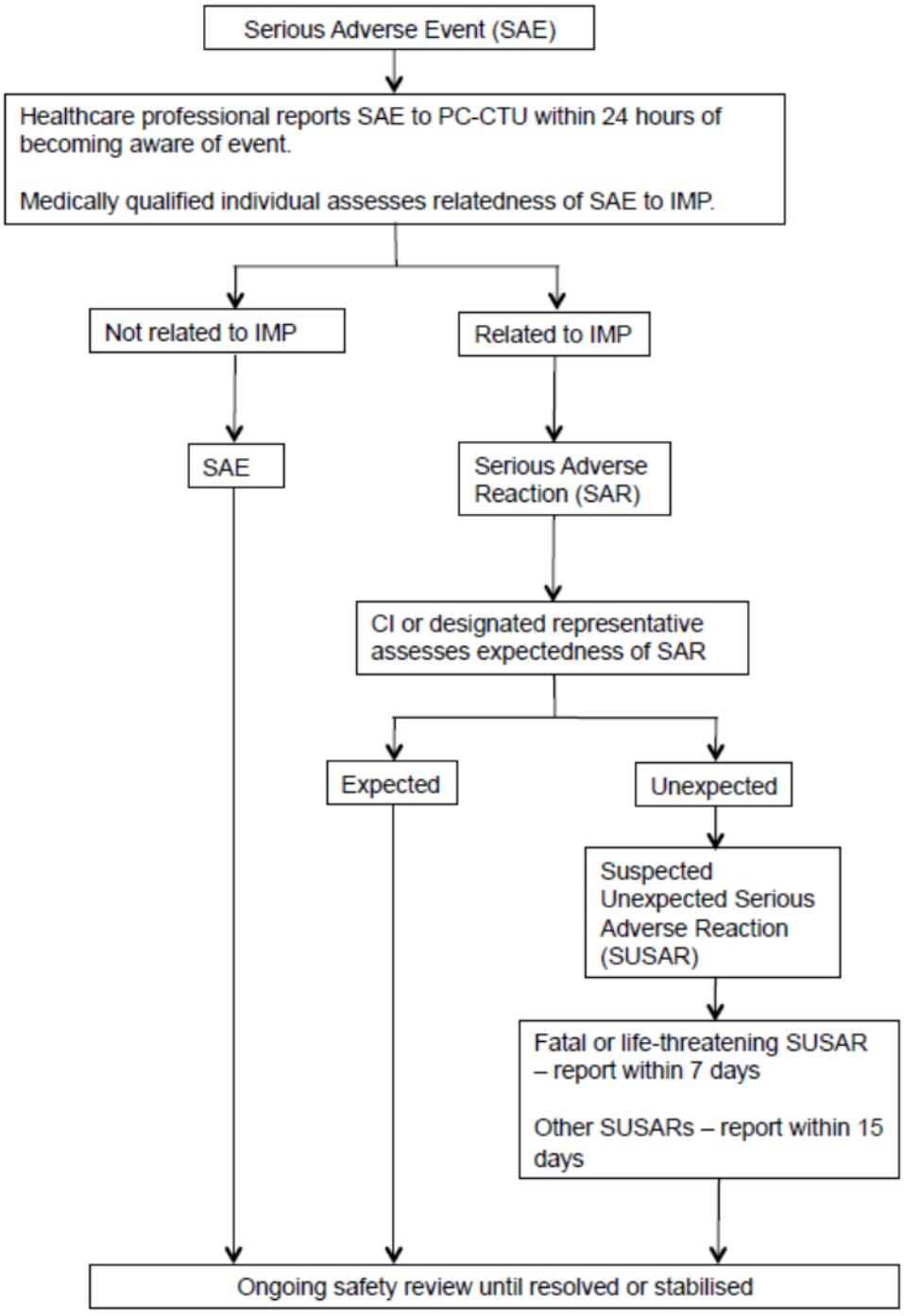


20. APPENDIX B: SCHEDULE OF PROCEDURES

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						
Duration of symptoms		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

21. APPENDIX C: SAE REPORTING FLOW CHART

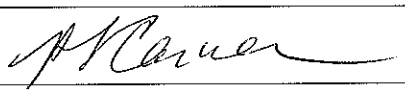


Primary Care
Clinical Trials Unit

FILE NOTE

FILE NOTE TITLE:	**Informed Consent Form- recording of version and date of PIS given and/or video viewed**	**File note ID/No.**	**05**
Study acronym or short title:	**ARCHIE**		
Investigator (Site Name):	**Kay Wang (University of Oxford)**		
Date:	**20 October 2014**		

The consent form was approved with no version and date relating to the patient information reviewed by the participant.
The version and date of the document used should be recorded in the space under point 1.
In addition, if the video was watched this can be recorded with the approximate date it was veiw.

	Name (Job title)	Signature	Date
Signed (Author of file note)	**Tricia Carver Senior Trial Manager**		**20 Oct 2014**
Reviewed by (if applicable)	**NA**	**NA**	
Approved by	**NA**	**NA**	

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.

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ARCHIE

ARCHIE ID

____/_____

EXAMPLE

Consent form

To be completed by parent/guardian of study participant

Study title: The early use of Antibiotics in at Risk Children with InfluEnza (ARCHIE)
Chief Investigator: Dr Kay Wang

*Please **write your initials** in the box beside each point.*

Your child may still participate in the study even if you do not agree to point 8.

1. I confirm that I have read and understood the information leaflet version number xx dated xx/xx/xx for the above study and have had the opportunity to ask questions, which have been answered satisfactorily. V2.2 1 Apr 2014 Video watched 29 Dec 2014 ☐
2. I understand that the participation of my child is voluntary and we are free to withdraw at any time, without giving any reason, without my child's medical care or legal rights being affected. ☐
3. I understand a nasal swab, and if possible, a throat swab, will be taken from my child and that these will be stored and used by the research team for further research and analysis. I consider all swab samples a gift to the University of Oxford and I understand my child will not gain any direct personal benefit from this. ☐
4. I understand my child's GP will be notified of my child's participation in the study. ☐
5. I consent to being contacted by the research team for the purposes of this study as outlined in the information leaflet. I understand that this will require me to provide the research team with my contact details and I confirm that I consent to this. ☐
6. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by responsible individuals from Universities of Oxford, Liverpool, Southampton or Bristol, or from the local NHS trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records and to extract relevant data in anonymised form for the purposes of this study. ☐
7. I consent for my child to participate in this study. ☐
8. Optional: I agree to allow my child to have throat swabs taken three months, six months and twelve months after entering this study and for non-cellular material from these swabs to be stored and used by the research team for further research and analysis. ☐

_____
Name of child (please print)

_____ _____ _____
Name of parent or legal guardian (Please print) Date Signature

_____ _____ _____
Name of person taking consent (Please print) Date Signature

TOP COPY for recruiting site*, MIDDLE COPY for parent/guardian, BOTTOM COPY for University of Oxford
***GP surgeries:* keep hard copy in site file and scanned copy in child's electronic medical record.**
***GP out-of-hours centres/Trust departments:* keep hard copy in site file and fax copy to child's GP surgery.**

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ARCHIE ID

__ __ __ / __ __ __ __

Consent form
To be completed by parent/guardian of study participant

Study title: The early use of Antibiotics in at Risk Children with InfluEnza (ARCHIE)
Chief Investigator: Dr Kay Wang

*Please **write your initials** in the box beside each point.*

Your child may still participate in the study even if you do not agree to point 8.

1. I confirm that I have read and understood the information leaflet version number xx dated xx/xx/xx for the above study and have had the opportunity to ask questions, which have been answered satisfactorily. ☐

2. I understand that the participation of my child is voluntary and we are free to withdraw at any time, without giving any reason, without my child's medical care or legal rights being affected. ☐

3. I understand a nasal swab, and if possible, a throat swab, will be taken from my child and that these will be stored and used by the research team for further research and analysis. I consider all swab samples a gift to the University of Oxford and I understand my child will not gain any direct personal benefit from this. ☐

4. I understand my child's GP will be notified of my child's participation in the study. ☐

5. I consent to being contacted by the research team for the purposes of this study as outlined in the information leaflet. I understand that this will require me to provide the research team with my contact details and I confirm that I consent to this. ☐

6. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by responsible individuals from Universities of Oxford, Liverpool, Southampton or Bristol, or from the local NHS trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records and to extract relevant data in anonymised form for the purposes of this study. ☐

7. I consent for my child to participate in this study. ☐

8. Optional: I agree to allow my child to have throat swabs taken three months, six months and twelve months after entering this study and for non-cellular material from these swabs to be stored and used by the research team for further research and analysis. ☐

Name of child (please print)		
Name of parent or legal guardian (Please print)	Date	Signature
Name of person taking consent (Please print)	Date	Signature

TOP COPY for recruiting site*, MIDDLE COPY for parent/guardian, BOTTOM COPY for University of Oxford
***GP surgeries:* keep hard copy in site file and scanned copy in child's electronic medical record.**
***GP out-of-hours centres/Trust departments:* keep hard copy in site file and fax copy to child's GP surgery.**

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ARCHIE ID
__ __ __ / __ __ __ __

Consent form for follow-up throat swabs
To be completed by parent/guardian of study participant

Study title: The early use of Antibiotics in at Risk Children with InfluEnza (ARCHIE)
Chief Investigator: Dr Kay Wang

When you gave consent for your child to take part in the ARCHIE study, you were unsure about whether to allow us to take optional follow-up throat swabs from your child.

These follow-up throat swabs will help us find out what types of infections your child might be carrying in his or her throat and how effective antibiotics might be at treating these infections in the future.

They will involve taking throat swabs from your child 3 months, 6 months and 12 months after they first joined the ARCHIE study (*i.e.* three throat swabs in total).

It is understood that you gave verbal consent over the telephone for your child to have these follow-up throat swabs, but we also need to record your consent in writing.

Please read the statement below. By signing this form, you are giving written consent for your child to have follow-up throat swabs.

I agree to allow my child to have throat swabs taken three months, six months and twelve months after entering the ARCHIE study and for non-cellular material from these swabs to be stored and used by the research team for further research and analysis.

Name of child (please print)		
Name of parent or legal guardian (Please print)	Date	Signature
Name of person taking consent (Please print)	Date	Signature

TOP COPY for recruiting site*, MIDDLE COPY for parent/guardian, BOTTOM COPY for University of Oxford
***GP surgeries:* keep hard copy in site file and scanned copy in child's electronic medical record.**
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ARCHIE ID

__ __ __ / __ __ __ __

Assent Form
To be completed by child (OPTIONAL)

Study title: The early use of Antibiotics in at Risk Children with InfluEnza (ARCHIE)
Chief Investigator: Dr Kay Wang

		Please Circle
1.	Have you read about this study?	YES/NO
2.	Has someone explained this study to you?	YES/NO
3.	Do you understand what this study is about?	YES/NO
4.	Have you asked all the questions that you want to?	YES/NO
5.	Have you had your questions answered in a way you understand?	YES/NO
6.	Do you understand it is okay to stop taking part at any time?	YES/NO
7.	Are you happy to take part in this study?	YES/NO

If any answers are 'no' or you don't want to take part, don't write your name!
If you do want to take part, write your name below

Name of child (please print)	Date

Name of person seeking assent (Please print)	Date	Signature

TOP COPY for recruiting site*, MIDDLE COPY for parent/guardian, BOTTOM COPY for University of Oxford
***GP surgeries:* keep hard copy in site file and scanned copy in child's electronic medical record.**
***GP out-of-hours centres/Trust departments:* keep hard copy in site file and fax copy to child's GP surgery.**

To find out more please visit our website:

www.archiestudy.com

or contact a member of the ARCHIE study team:

Tricia Carver—Trial Manager

Dr Kay Wang—Principal Investigator

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This study is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme
(Grant Reference RP-PG-1210-12012)

ARCHIE

The early use of Antibiotics in 'at Risk' CHildren with InfluEnza

Archie is more ill than usual when he just gets a cold or flu……..

…… but I'm not sure he is ill enough to need antibiotics

Sounds familiar?

www.archiestudy.com

Why are we doing the ARCHIE study?

We would like to find out whether giving an antibiotic called co-amoxiclav to 'at risk' children aged 6 months to 12 years early on when they have flu or flu-like illness might:

1. Help stop them from developing bacterial infections and becoming more unwell.
2. Help them get better more quickly.
3. Affect how well antibiotics work against similar infections in future.

'At risk' children with a long-term medical condition or disability are particularly prone to developing bacterial infections if they get flu or a flu-like illness.

What will happen if my child and I decide to take part?

Your doctor or nurse will:

- Ask you some questions about your child's flu-like illness
- Test to see whether your child has the flu virus by taking a swab from his/her nose
- Test to see whether you child has any bacterial infections by taking a swab from his/her throat
- Give your child a 5-day course of medication (either co-amoxiclav or a 'placebo' which looks & tastes the same but does not contain the antibiotic)
- Give you a study diary to fill in

www.archiestudy.com

What is co-amoxiclav?

Co-amoxiclav is a type of penicillin antibiotic. It has a wider effect than ordinary penicillin and is used to treat many types of bacterial infections in children like chest, ear, throat and sinus infections.

At the moment, co-amoxiclav is not licensed to treat children early on in a flu-like illness to try and prevent them from coming down with bacterial infections.

The ARCHIE study will help us to find out whether co-amoxiclav can help 'at risk' children in this way.

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ARCHIE

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The early use of Antibiotics in at Risk CHildren with InfluEnza

Information leaflet for parents and guardians

1Apr14 v2.2
REC 13/NW/0621

We would like to invite you and your child to take part in the ARCHIE study.

This information leaflet explains why we are doing this research study and what it will involve for you and your child if you decide to take part. Please read it carefully before making your decision. Please ask if you have any questions.

Why have my child and I been invited to take part?

We would like to invite you and your child to take part in the ARCHIE study because your child is unwell with a flu-like illness which started within the last 5 days.

Your doctor or nurse thinks that your child has more than just a simple cough or cold, but does not have any obvious signs at the moment of a bacterial infection which needs to be treated with antibiotics. Bacterial infections can cause chest, ear, throat or sinus infections, which can make children feel more unwell. Children who get flu (also called influenza) are more prone to developing bacterial infections than children who get other types of viral infections.

'At risk' children with a long-term medical condition or disability are particularly prone to developing bacterial infections if they get flu or a flu-like illness. 'At risk' children include children with lung problems (*e.g.* asthma), type 1 or type 2 diabetes, cerebral palsy, Down's syndrome, cancer, kidney problems, heart problems and problems with the immune system. Even though the 'flu jab' (flu vaccination) helps protect these children against some types (strains) of flu, other types of flu and viruses similar to flu can still cause flu or flu-like illness.

Why are we doing the ARCHIE study?

We would like to find out whether giving an antibiotic called co-amoxiclav to 'at risk' children (aged 6 months to 12 years) early on when they have flu or flu-like illness might:

1. Help stop them from developing bacterial infections and becoming more unwell.
2. Help them get better more quickly.
3. Affect how well antibiotics work against similar infections in future.

When children first start feeling unwell, it can be difficult for doctors and nurses to tell whether they are in the early stages of a bacterial infection which might need to be treated with antibiotics. Doctors and nurses often see children who have more than just a simple cough or cold, but do not have obvious signs of a bacterial infection. Sometimes they give these children antibiotics 'just in case'. However, some of these children might have got better just as quickly without them. Giving antibiotics to children who do not need them may change the types of bacteria we find in their nose and throat and affect how well similar antibiotics work against infections in the future.

What is co-amoxiclav?

Co-amoxiclav (also known as 'Augmentin') is an antibiotic which contains a type of penicillin antibiotic. Co-amoxiclav is effective against more types of bacterial infection than ordinary penicillin antibiotics and is already licensed and commonly used to treat many types of infections in children. These include chest, ear, throat and sinus infections.

At the moment, co-amoxiclav is not licensed to prevent children, who see their doctor or nurse early on in a flu-like illness, from coming down with bacterial infections.

The ARCHIE study will help us find out whether co-amoxiclav can be used to help 'at risk' children in this way.

What will happen if we decide to take part?

If you and your child decide to take part, you will need to fill in and sign a consent form. If your child wants to, they may also fill in a form to say they are willing to take part.

Your doctor or nurse will then:

- Ask you some questions about your child's flu-like illness.
- Take a nose swab and a throat swab from your child.
- Give you some study medication for your child.
- Give you a study diary to fill in.

Your child's swabs

- If possible, your doctor or nurse will take two swabs from your child: one from the nose and another from the back of the throat.
- Your child's swabs will be sent to the laboratories of the Alder Hey Children's Hospital in Liverpool. The nose swab will be tested to see if your child has any respiratory viruses. The throat swab will be tested to see if your child has any respiratory bacteria.
- If you think that it won't be possible for your doctor or nurse to take a throat swab from your child, you and your child can still take part in the rest of the study. However, you and your child will not be able to take part if it won't be possible to take a nose swab from your child.
- Your child's nose swab may tickle a bit and the throat swab may make him or her 'gag' momentarily. However, this is normal and will not hurt your child. You will be able to

comfort and support your child while the doctor or nurse is taking his or her swabs.

Your child's study medication

- Your child's study medication will either be the antibiotic (co-amoxiclav) or a 'placebo' and will be given to you in liquid form. A placebo is an inactive preparation which is otherwise identical to the medication being studied. In this study, the placebo liquid will look and taste the same as the antibiotic liquid, but will **not** contain the antibiotic itself.
- We will ask you to give your child his or her study medication twice a day for five days. Please ask your doctor or nurse to advise you if your child does not usually swallow medication.
- The type of study medication your child is given will be decided by chance, like a coin toss, and not by your doctor or nurse. Neither you nor your doctor or nurse will know whether your child has been given the antibiotic or the placebo liquid.
- The research team will also not know which type of study medication your child has been given until after the end of the study. They will only be told this sooner if any issues arise before the end of the study, which could affect the safety of children taking part.
- This is a normal part of research studies like ours. By giving some children the placebo liquid and others the antibiotic, we will be able to find out whether the antibiotics themselves really work.

What side-effects might my child get from the study medication?

- Most children will not have any side-effects from the antibiotic. However, up to 1 in 10 might get minor side-effects such as a slight stomach upset (feeling sick, vomiting or diarrhoea) or thrush (a type of fungal infection). Other less

common side-effects include skin rashes, dizziness and headaches.
- Unexpected serious allergic reactions can very rarely occur with symptoms such as lip swelling, throat tightness and difficulty breathing. If this happens, please seek medical advice immediately, or go to hospital or call for an ambulance if your child is very unwell.

What if my child gets the placebo?

- If your child gets the placebo, this does not mean that he or she will definitely get worse or develop a bacterial infection.
- If your doctor or nurse had felt that your child needed antibiotics straightaway, he or she would not have invited you to take part in the ARCHIE study.
- Whatever type of medication your child gets, a doctor or nurse or someone from the research team will give you a call one week and two weeks after your child enters the study to ask you how your child is. However, please seek advice from your doctor or nurse or take your child to hospital sooner if you think he or she is becoming more unwell.

Your study diary

We will ask you to fill in a diary about your child's flu-like illness and any complications which arise from this. In your diary, we will ask you to record:

- your child's symptoms (*e.g.* cough, shortness of breath, disturbed sleep).
- your child's temperature (we will provide you with an armpit thermometer).
- when you give your child study medication and any other medication.
- any side-effects your child has from the study medication.

- any time you take off from work, and any time that your child takes off from school or nursery.
- any visits or telephone calls with a doctor or nurse.
- your child's overall wellbeing after 4 days, 1 week, 2 weeks and 4 weeks. We can send you reminders by text or e-mail.

Your child may also fill in some questionnaires about him or herself – we will let you and your child decide this together.

We will phone you after one week and two weeks

Your doctor or nurse or a member of the research team will ask you if you have had to seek medical advice or go to hospital because of your child's flu-like illness or complications of this. They will also check with you if your child has had any side-effects from his or her study medication.

We will review your child's medical notes

We will collect some information from your child's medical notes about your child's health, medications, vaccinations and visits or telephone calls with a doctor, nurse or other healthcare professional.

We will ask you for permission to take extra swabs from your child

We will ask you if we can take three more throat swabs from your child once he or she is feeling better: one swab after 3 months, another after 6 months and a final swab after 12 months.

These swabs will help us find out what types of infections your child might be carrying in his or her throat and how effective antibiotics might be at treating these infections in the future. Your child may still take part in the rest of our study even if you

decide not to let us take these extra swabs. Please let your doctor or nurse know what you decide.

Thank you for reading about our study. If you are still interested in taking part, please read on for further information….

Do I have to allow my child to take part?

No. It is entirely up to you, and you can change your mind at any time without giving a reason. If you decide not to take part, or agree but later change your mind, you and your child will still receive the same standard of medical care.

What are the possible benefits and disadvantages of taking part?

This study will help us work out whether giving antibiotics to 'at risk' children early on when they have flu or flu-like illness is worthwhile. It may also help the government plan how to use antibiotics during future flu epidemics or pandemics (which is when lots of people get flu all at once).

Giving your child his or her study medication and completing your study diary will take some of your time, around 5 to 10 minutes a day. However, all the information we ask you for is important, so please try and complete as much as you can, even if you cannot complete everything.

The study medication may help your child get better more quickly and/or prevent your child from becoming more unwell from a bacterial infection. However, we will not know this for sure until the end of the study.

What will happen to the information about my child?

The research team have a duty of confidentiality to your child as a research participant. All data will be kept securely according to the Data Protection Act 1998. Responsible people from the Universities of Oxford, Liverpool, Bristol or Southampton, the NHS Trust or the Medicines and Healthcare Products Regulatory Agency (MHRA) may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. Your child's GP will be informed that your child is taking part in the study and they will be given a copy of the signed consent form for their records.

Non-cellular material from your child's swabs will be stored securely and confidentially in the specialist laboratories and continue to be stored there after our study has finished for use in further research. This will help the laboratories study better ways of finding infections and working out how likely they are to get better with antibiotics in the future.

What will happen if I don't want my child to carry on with the study?

If you decide you no longer wish your child to take part in our study, please let your doctor or nurse know. Alternatively, you can phone, write to or e-mail the study co-ordinator. You and your child can withdraw from the study at any time without giving a reason.

What will happen to the results of the study?

The results will be published in a scientific journal and on our website www.archiestudy.com for you to read.

Who is organising and funding the research?

This research study is part of a series of research studies known as the ARCHIE programme (The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care). The ARCHIE programme is funded by the National Institute for Health Research. The University of Oxford is the Research Sponsor.

What will happen if there is a problem or something goes wrong?

The University of Oxford has arrangements in place in case of harm arising from participation in a study for which it is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment which is provided. If you wish to complain about any aspect of the way in which you have been approached or treated during this study, you should contact the study co-ordinator or the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224. You may also contact the head of the CTRG office by e-mail, ctrg@admin.ox.ac.uk.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect patients' safety, rights, wellbeing and dignity. This study has been reviewed and approved by the NRES Committee North West - Liverpool East.

Thank you for reading this leaflet.

Please ask us if you have any questions.

Our contact details

www.archiestudy.com

Nuffield Department of Primary Care Health Sciences

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Radcliffe Observatory Quarter

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Oxford, OX2 6GG

Tel: 01865 617 842
Email: archie@phc.ox.ac.uk

Dr Kay Wang, Lead Investigator
Tricia Carver, Trial Manager

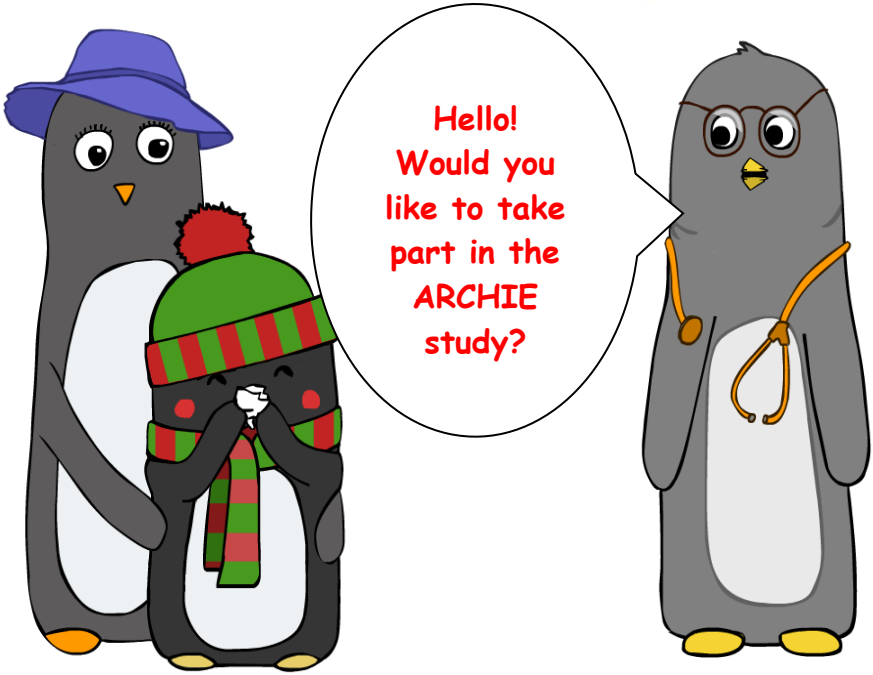
This study is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme

(Grant Reference RP-PG-1210-12012)

NHS
National Institute for Health Research

The early use of Antibiotics in at Risk CHildren with InfluEnza

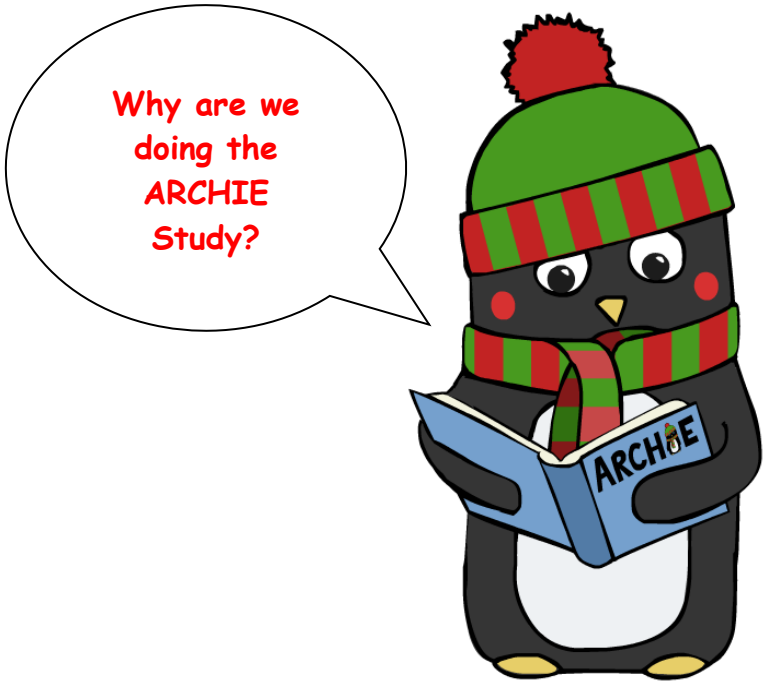
ARCHIE



Information for Children

UNIVERSITY OF OXFORD

REC 13/NW/0621



We are doing the ARCHIE study to try and find out how we can help children when they are ill with the flu. Flu is a germ which can make you ill by giving you a cough or cold. Most of the time, coughs and colds get better by themselves, but flu can be a bit different.

Sometimes children with flu pick up other germs as well. These germs can make them feel more ill and need to go back to see their doctor or nurse.

We would like to find out whether giving children with flu a type of medicine called an ‘antibiotic’ can help them get better faster. An ‘antibiotic’ is a type of medicine which doctors and nurses give people when they have chest infections, ear infections or other germs which make them feel ill.

Your doctor or nurse will:

1. Ask you how you have been feeling since you got the flu.
2. Take a swab from your nose and, if possible, one from your throat. This won't hurt, but it might tickle a bit.

3. Give you some medicine to take. The medicine is a liquid, so it should be easy for you to swallow.

4. Ask your Mum, Dad or carer to take your temperature each day until you feel better and fill in a diary about you.

If you like, you can also answer some questions to tell us how you are feeling. Your doctor or nurse will ask if it is OK to take some more swabs from you in a few months' time. You should be feeling better by then.

What will my medicine be?

Your medicine will be an antibiotic or a 'placebo'. The placebo will be a liquid which looks and tastes just like the antibiotic but does not have the antibiotic in it. We are giving some children the antibiotic and some children the placebo so that we will know whether the antibiotics really work. To make things fair, the type of medication you get will be decided at random and your doctor or nurse will not know which type of medicine they are giving you.

Is it safe to take part?

Your doctor or nurse will check that it is safe for you to take part. Your doctor or nurse or someone from the ARCHIE study team will also check how you are after one week, and again after two weeks by phoning your Mum, Dad or carer. But if you are not feeling well at **any** time, please tell your Mum, Dad or carer, and ask them to take you to see a doctor or nurse.

What if there is a problem?

If you are not happy with something about the study, please tell us or ask your Mum, Dad or carer to tell us.

Do I have to take part?

No, you don't have to take part, but you may want to talk to your Mum, Dad or carer before making up your mind.

Will anyone else know I am doing this?

Yes, we will tell your doctor.

What will happen if I want to stop doing the study?

If you want to stop doing the study at any time, please tell your doctor or nurse or get your Mum, Dad or carer to tell them. No one will be cross with you if you decide you want to stop.

What will happen to the results of the study?

We will put the results on our website www.archiestudy.com for you to read.

Thank you for reading this! We hope you feel better soon!

Our contact details

www.archiestudy.com

Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Tel: 01865 617 842
Email: archie@phc.ox.ac.uk

Dr Kay Wang, Lead Investigator
Tricia Carver, Trial Manager

This study is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme
(Grant Reference RP-PG-1210-12012)

NHS
National Institute for Health Research

Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Direct line: 01865 617 842
FAX: 01865 617 939

Please access the participant information videos using the You tube links:

How can I find out more about the ARCHIE study
https://www.youtube.com/watch?v=3cWfQeBkGus

What would taking part involve?
https://www.youtube.com/watch?v=teU9FMrcadw

If we decide to take part in the ARCHIE study, will this involve any follow-up research?
https://www.youtube.com/watch?v=jTdWCIpXIxw

How can I find out more about ARCHIE?
https://www.youtube.com/watch?v=utxB8Zjewx8

The early use of Antibiotics in 'at Risk' CHildren with InfluEnza

ARCHIE

www.archiestudy.com

I might be interested in letting my child join the ARCHIE Study if they get flu

Child's Name:______________________________

Child's date of birth:_______________________

Please leave your completed slip at reception so we can record your interest.

Interest card 9Aug13 v1 REC13/NW/0621

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The early use of Antibiotics in 'at Risk' CHildren with InfluEnza

Asthma

Diabetes

Cerebral palsy

Cancer or immune system problems

Archie is more ill than usual when he just gets a cold or flu……

……but I'm not sure if he is ill enough to need antibiotics.

Down's syndrome

Sickle cell disease

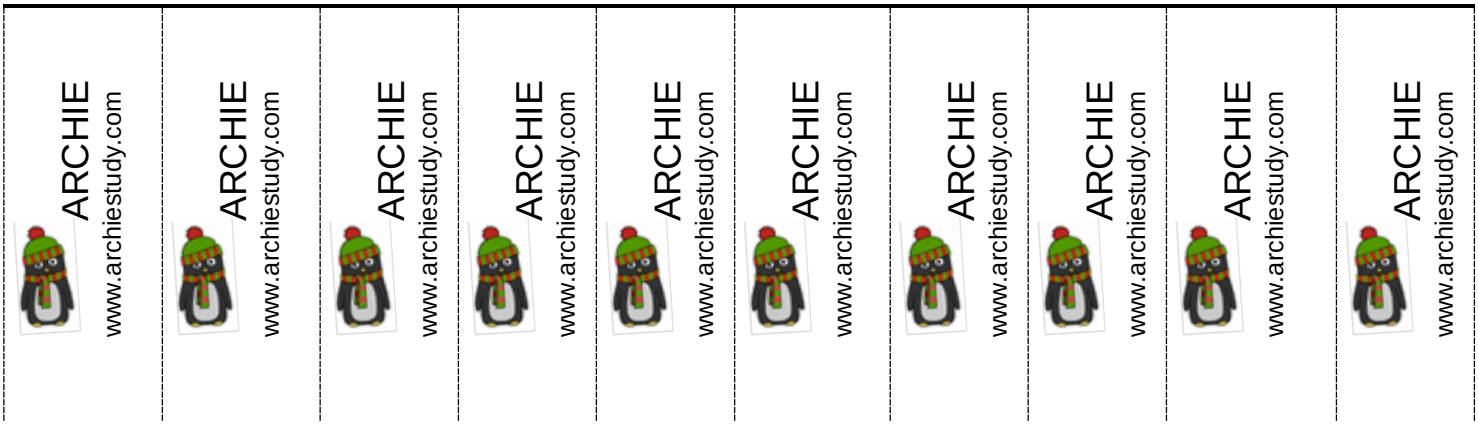
Heart, kidney or liver problems

Premature baby

Sounds familiar?

If your child is aged 6 months to 12 years and has a long-term medical problem, we would like to invite you to take part in the ARCHIE study if your child gets flu this winter.

24Jan14 v1.1 REC 13/NW/0621



The early use of Antibiotics in 'at Risk' CHildren with InfluEnza

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www.archiestudy.com

Does your child have any of the following?

- Lung problems (*e.g.* asthma)
- Diabetes (type 1 or type 2) or other metabolism problems
- Born prematurely and under 2 years of age
- Neurological disability (*e.g.* cerebral palsy)
- Genetic problems (*e.g.* Down's syndrome)
- Heart problems (*e.g.* congenital heart disease)
- Kidney problems (*e.g.* chronic kidney disease)
- Liver problems (*e.g.* chronic hepatitis)
- Immune system problems (*e.g.* HIV infection, on steroids or chemotherapy)
- Sickle cell disease

If so, you and your child may be interested in taking part in the ARCHIE study if your child gets flu this winter.

Children with any of the problems listed above are at greater risk of complications from flu or flu-like illness than otherwise healthy children.

We are doing the ARCHIE study to find out whether giving antibiotics to these 'at risk' children **within the first 5 days of developing flu-like symptoms** can help stop them from becoming more unwell from bacterial infections, such as chest infections and ear infections.

To find out more or register your interest in taking part, please visit our website or talk to your doctor or nurse.

UNIVERSITY OF OXFORD

NHS National Institute for Health Research

This study is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference RP-PG-1210-12012)

Print on department headed letter paper

The early use of Antibiotics in at Risk CHildren with InfluEnza

This study is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference RP-PG-1210-12012)

Dear Dr _____,

RE:
Name of patient:
Patient's date of birth:

This patient was entered into the ARCHIE trial on (insert date): _____ at

(insert location or stamp):_____

GP walk-in centre/Hospital department (delete as appropriate).

The ARCHIE trial is a double-blind randomised placebo-controlled trial to determine whether giving a five-day course of co-amoxiclav to 'at risk' children at an early stage during an influenza-like illness reduces the likelihood of them needing to re-consult due to clinical deterioration. For further details, please see the study website:

www.archiestudy.com

Please record the following details in your patient's medical notes:

Site ID: _____

ARCHIE ID: _____

Medication ID: _____

Please find enclosed a copy of your patient's consent form. Please retain this in your patient's medical record.

Please note that your patient's parent/guardian has given consent for us to gather information from your patient's medical notes. A member of the ARCHIE research team will contact you to arrange a suitable time and way of doing this.

Please get in touch with us if you have any questions.

Many thanks.
The ARCHIE team

Instructions for healthcare professional recruiting patient:

Please fax this letter to the patient's GP **and** to the ARCHIE team (01865 617 939).
Please keep the original letter in your site file.

Email message:

Dear XX,

Thank you for taking part in the ARCHIE study. We hope your child is feeling better.

Insert as appropriate:
Please fill in your day 4 questionnaire today.
OR
Please remember to complete and return your Week X Study Diary to us (archie@phc.ox.ac.uk).

Please tell your GP surgery if you have any concerns or if you think your child has had any side-effects from the study medication and remember to record these in your diary.

Many thanks.
The ARCHIE study team.

The early use of Antibiotics in at Risk Children with InfluEnza

Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Direct line: 01865 617 842
FAX: 01865 289 412

Text message reminders:
Day 4: Hello from the ARCHIE study team. Please fill in your day 4 questionnaire today. You will find this on pages 6 and 7 of your Week 1 Study Diary. Thank you!

Day 7: Hello from the ARCHIE study team. We will be calling you today for your week 1 follow-up. Please remember to complete and return your Week 1 Study Diary to us (archie@phc.ox.ac.uk). Thank you!

Day 14: Hello from the ARCHIE study team. We will be calling you today for your week 2 follow-up. Please remember to complete and return your Week 2 Study Diary to us (archie@phc.ox.ac.uk). Thank you!

Day 21: Hello from the ARCHIE study team. Please remember to complete and return your Week 3 Study Diary to us (archie@phc.ox.ac.uk). Thank you!

Day 28: Hello from the ARCHIE study team. Please remember to complete and return your Week 4 Study Diary to us (archie@phc.ox.ac.uk). Thank you!

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

________________________is taking part in the ARCHIE study (www.archiestudy.com) and was given study medication (co-amoxiclav or placebo) to take for 5 days starting on ___ /___ /____.
Archie ID: ______ /_______
Medication ID: ______________________ cc 14May14 v2.1

REC: 13/NW/0621

Information for clinicians: If you think this child has had an adverse reaction to his/her study medication:

- Please **STOP** the study medication.
- Please prescribe a **non beta-lactam antibiotic** if antibiotics are clinically indicated.
- Please see our website for instructions on reporting **suspected adverse reactions to study medication**.

Local investigator:

Contact telephone number: 01865 617 842 (trial office)

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ARCHIE

The early use of Antibiotics in 'at Risk' CHildren with InfluEnza

Awesome Attitude

This certificate is awarded to

_____

for your special contribution to the ARCHIE Research Programme

UNIVERSITY OF OXFORD

UNIVERSITY OF LIVERPOOL

University of BRISTOL

UNIVERSITY OF Southampton

NHS National Institute for Health Research

ELIGIBILITY ASSESSMENT

INCLUSION CRITERIA	*Please circle*	EXCLUSION CRITERIA	*Please circle*
Aged 6 months to 12 years inclusive	**YES/NO**	Known contraindication to co-amoxiclav**	**YES/NO**
In 'at risk' category**	**YES/NO**	Child given antibiotics within the last 72 hours	**YES/NO**
Presenting with influenza-like illness (*i.e.* cough and fever*) during influenza season	**YES/NO**	Child requires immediate antibiotics or hospital admission (clinician's judgement)	**YES/NO**
Presenting within 5 days of symptom onset	**YES/NO**	Presence of any reason to prevent healthcare professional from obtaining high nasal swab	**YES/NO**
Permanently registered at a general practice in England	**YES/NO**	Child with known cystic fibrosis	**YES/NO**
Parent/guardian able to complete study diary and questionnaires	**YES/NO**	Child previously entered into the ARCHIE study	**YES/NO**
		Child has been involved in another medicinal trial within the last 90 days	**YES/NO**
All INCLUSION CRITERIA must be YES AND all EXCLUSION CRITERIA must be NO for the child to be eligible to enter the study.			

*** Fever reported by child or parent/guardian OR temperature 37.9°C or more.**
**** Full details on study website (www.archiestudy.com) and in your investigator site file.**

Screening information:

Date assessed: _____ Site:_____ Assessor:_____
(Day/Month/Year) (*e.g.* site stamp) (initials)

1. Is the child eligible to enter the study? **YES/NO**

IF NO – Please explain this to the child's parent/guardian and thank them for their time. Please also record the child's screening ID and details on your screening log.
IF YES – Please explain the study to the child's parent/guardian and go to point 2.

2. Has the child's parent or guardian given consent for the child to enter the study? **YES/NO**

IF NO – Please thank them for their time. Please also record the child's screening ID and details on your screening log.
IF YES – Please go to point 3.

3. Please assign the child an ARCHIE ID (you will find this on the front cover of your study pack). :

___ ___ ___ / ___ ___ ___ ___

ARCHIE ID

Please record the child's ARCHIE ID, along with his/her screening ID and other details on your screening log.

Definition of 'at risk' categories

The following 'at risk' categories are intended as a guide to identify children who are likely to be at greater risk of influenza-related clinical deterioration or complications. Please contact the study team if you are unsure whether a child is 'at risk'.

Category	Definition
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 within the last 12 months. Recurrent viral wheeze (3 or more episodes within the last 12 months). Bronchopulmonary dysplasia.
Cardiac	Congenital heart disease or 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 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 20 kg).
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/1.73m^2 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/1.73m^2 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).

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 (*i.e.* 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)).
- Known or suspected infectious mononucleosis.
- Known lymphocytic leukaemia.
- Known phenylketonuria.
- eGFR less than 30 ml/min/1.73m^2 (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).

__ __ __/__ __ __ __

ARCHIE ID

CONTACT INFORMATION

1. PARTICIPANT DETAILS

Surname	
First name(s)	
NHS number	

2. CONTACT DETAILS FOR PARTICIPANT'S GP

GP name	
GP surgery address	
GP surgery telephone number	

BASELINE ASSESSMENT FORM

ARCHIE

__ __ __ / __ __ __ __

ARCHIE ID

CHILD'S BASELINE DETAILS

Please tick to confirm that child meets eligibility criteria AND parent/guardian has signed consent form: ☐

Date of study entry (day 1) D D M M Y Y Y Y Sex: M ☐ F ☐

Date of birth D D M M Y Y Y Y Smoker(s) in household: YES ☐ NO ☐

Received **this season's** seasonal influenza vaccination? YES ☐ NO ☐ NOT KNOWN ☐

Receive d **last season's** seasonal influenza vaccination? YES ☐ NO ☐ NOT KNOWN ☐

AT RISK CATEGORIES (please tick all that apply):

Respiratory ☐ Neurological ☐ Liver ☐

Cardiac ☐ Renal ☐ Immunodeficiency ☐

Other (please state) ☐ ……..

CURRENT INFLUENZA-LIKE ILLNESS EPISODE (as reported by parent/guardian)

Date symptoms started D D M M Y Y Y Y

Date fever started D D M M Y Y Y Y

MEDICATIONS TAKEN BY CHILD DURING CURRENT INFLUENZA-LIKE ILLNESS EPISODE

Antivirals (*e.g.* oseltamivir) If **YES**, give name(s) of antiviral(s):	YES ☐	NO ☐	NOT KNOWN ☐
Antipyretics (*e.g.* paracetamol) If **YES**, give name(s) of antipyretic(s): Date (DD/MM/YYYY) and time (hh:mm) of most recent dose.	YES ☐ _ _/_ _/_ _ _ _	NO ☐ _ _:_ _ am/pm (please circle)	NOT KNOWN ☐
Other medications If YES, give name(s) of medication(s):	YES ☐	NO ☐	NOT KNOWN ☐

PHYSICAL EXAMINATION

Temperature: _____°C Time temperature taken: ___:___ am/pm (please circle)

Heart rate: _____ beats per minute Respiratory rate: _____ breaths per minute

Weight : _____ kg

SWABS

High nasal swab taken? YES ☐ NO ☐ Throat swab taken? YES ☐ NO ☐

STUDY MEDICATION – Please write participant's study medication ID and dose in the yellow box

Please go to www.archiestudy.com to generate the child's study medication ID number. You will need to enter the child's age, weight and current influenza vaccination status.

Study medication ID: __ __ __ __ __ __ Study medication dose: _____ ml twice daily for 5 days

QUESTIONNAIRES TO BE COMPLETED DURING BASELINE APPOINTMENT

By parent/guardian (compulsory):

1. EQ-5D-Y proxy YES ☐ NO ☐ 2. CARIFS YES ☐ NO ☐

By child (optional):

EQ-5D-Y YES ☐ NO ☐

Please tick to confirm study pack given and explained: ☐

EQ-5D-Y (baseline) - to be completed by child (OPTIONAL)

__ __ __ / __ __ __ __

ARCHIE ID

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility *(walking about)*

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

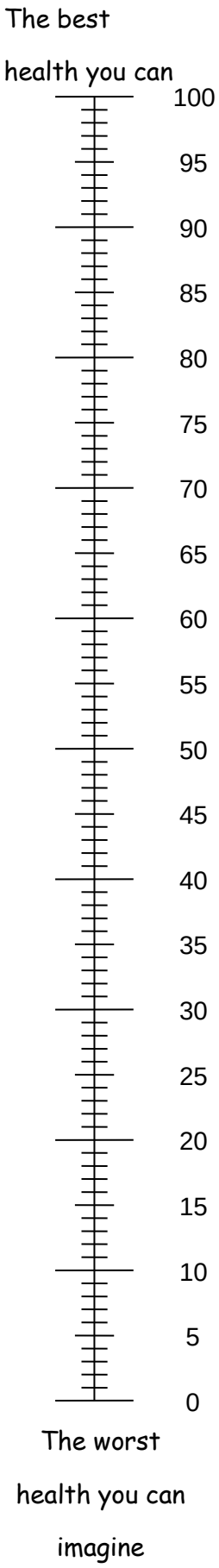
I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.



EQ-5D-Y proxy (baseline) - to be completed by parent/guardian

__ __ __ / __ __ __ __

ARCHIE ID

Describing the child's health today

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think **the child** would mark to describe his/her own health **TODAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she has no problems walking about ❑
He/she has some problems walking about ❑
He/she has a lot of problems walking about ❑

Looking after myself

He/she has no problems washing or dressing him/herself ❑
He/she has some problems washing or dressing him/herself ❑
He/she has a lot of problems washing or dressing him/herself ❑

Doing usual activities (for example. *going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑
He/she has some problems doing his/her usual activities ❑
He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑
He/she has some pain or discomfort ❑
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy ❑
He/she is a bit worried, sad or unhappy ❑
He/she is very worried, sad or unhappy ❑

How good is the health of the child TODAY

- We would like to know how good or bad you think **the child** would rate **his/her** own health TODAY

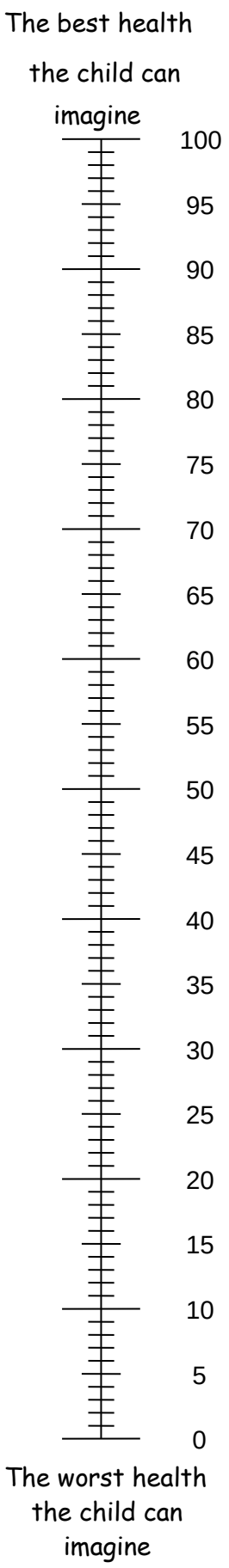
- This line is numbered from 0 to 100

- 100 means the <u>best</u> health the child can imagine

  0 means the <u>worst</u> health the child can imagine

Please, mark an X on the line that shows how good or bad you think **the child** would rate **his/her** health TODAY

Now, please write the number you marked on the scale in the box below.



CARIFS (baseline) - to be completed by parent/guardian

__ __ __ / __ __ __ __

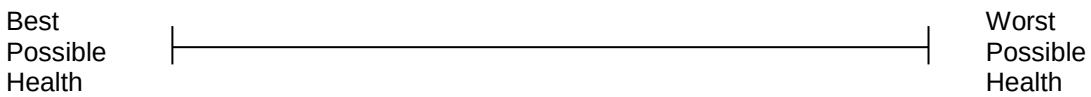
ARCHIE ID

How much of a problem have the following symptoms been for your child today?

Please tick ONE box for each symptom**.**

	Symptom	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know or Not Applicable
1	Poor appetite					
2	Not sleeping well					
3	Irritable, cranky, fussy					
4	Feels unwell					
5	Low energy tired					
6	Not playing well					
7	Crying more than usual					
8	Needing extra care					
9	Clinginess					
10	Headache					
11	Sore throat					
12	Muscle aches and pains					
13	Fever					
14	Cough					
15	Nasal congestion, runny nose					
16	Vomiting					
17	Not interested in what's going on					
18	Unable to get out of bed					

Please mark on this line how sick your child is today:



The early use of
Antibiotics in 'at Risk' CHildren with InfluEnza

My Study Diary

Study Site ID: _____

Archie ID: _____

I have taken my ARCHIE study medicine!

You will be taking your study medicine 2 times a day for 5 days.
Archie will help you keep track if you put a sticker on a balloon each time you take your study medicine.

How are you feeling?

Please draw the mouth on the face to tell us how you are feeling each day.

Back to Normal, or A Little Unwell, not quite back to normal, or Unwell

Archie has special tasks for you on days 4, 7, 14 and 28. You may need an adult to help you.

Day 1	Day 2	Day 3	**Day 4** Please go to pages 4 and 5 and answer the questions	Day 5	Day 6	**Day 7** Please go to pages 6 and 7 and answer the questions
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	**Day 14** Please go to Pages 8 and 9 and answer the questions
Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	**Day 28** Please go to pages 10 and 11 and answer the questions

Day 4

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility *(walking about)*

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

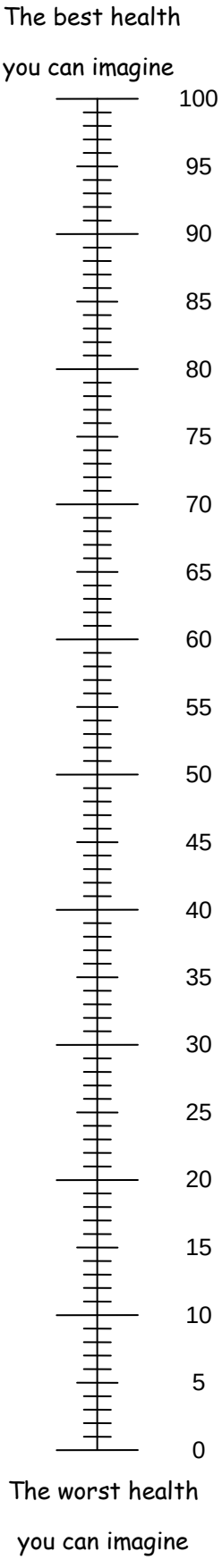
I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.



Day 7

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility *(walking about)*

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

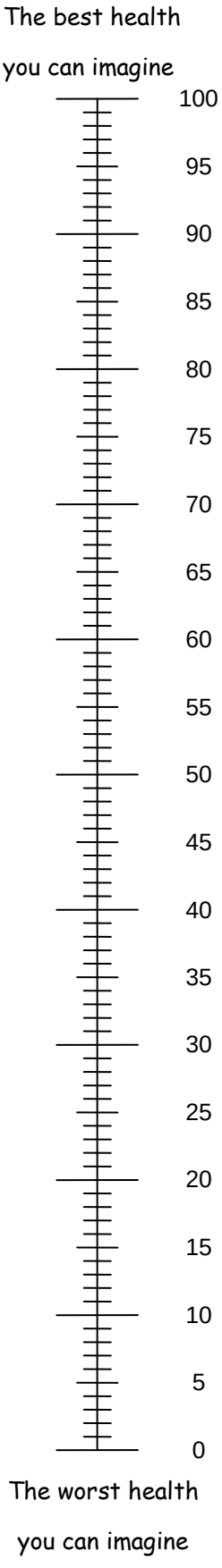
I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.



Day 14

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility *(walking about)*

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

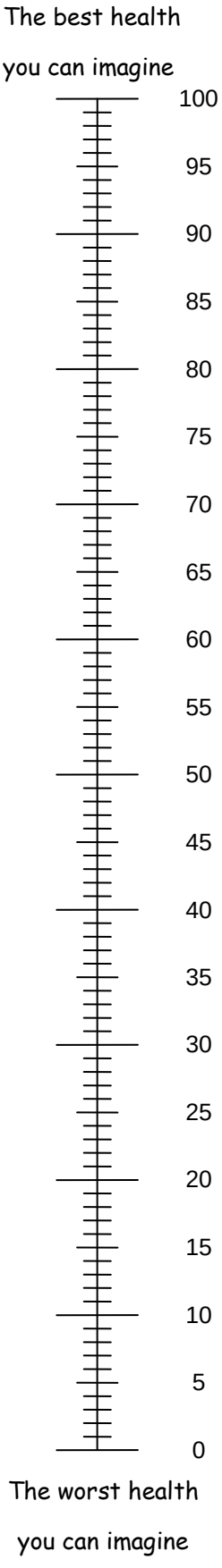
I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.



Day 28

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility *(walking about)*

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

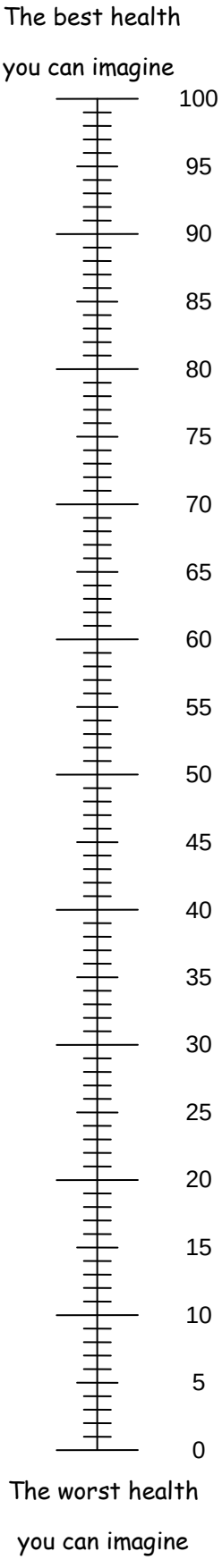
I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.



Thank you very much for taking part in our important research.

Please send us your finished diary so we can send you an official certificate for helping us with the ARCHIE study. Well done!

The early use of
Antibiotics in 'at Risk' CHildren with InfluEnza

Study Diary – Week 1

Archie ID: _____

To be completed by healthcare professional:

Day of study entry (day 1): Day of week_____Date (dd/mm/yyyy)_____

Key days to remember for filling in this diary:

Day 4	Day of week_____Date (dd/mm/yyyy)_____
Day 7	Day of week_____Date (dd/mm/yyyy)_____

Medication dose: _____

Medication timings (approximate):

Morning dose to be given at (hh:mm): _____

Evening dose to be given at (hh:mm): _____

IMPORTANT INFORMATION

Please DO NOT give your child more than 10 doses of study medication.

Please discard any unused study medication after you have given your child 10 doses.

UNIVERSITY OF OXFORD

WEEK 1 DIARY CONTENTS

Thank you for agreeing to fill in this diary for your child. Please try to fill it in at the end of each day. Please complete as much information as you can, but don't worry if you miss something by mistake – just keep going!

Contents	When should I fill this in?	Tips and advice
Your child's symptoms	Days 1 to 7	You can stop filling in your child's symptoms once your child has scored '0' for every symptom for two days in a row.
Your child's temperature	Days 1 to 7	Please take your child's temperature at bedtime OR before giving you child medicine to lower his/her temperature (*e.g.* paracetamol, ibuprofen), whichever happens first. Please also write down the time you took your child's temperature. You can stop filling in your child's temperature once it has been 37.4 degrees or below for two days in a row.
Your child's study medication	Days 1 to 6	Please record each dose of study medication you give your child. **Please do not give your child more than 10 doses in total.**
Other medication for your child's flu-like illness	Days 1 to 7 (if applicable)	Please write down any additional medicines you give to your child for his/her flu-like illness or any complications of this. This includes higher doses of your child's usual medications.
Day 4 study questionnaire	Day 4 (Pages 6-7)	Please fill this in on day 4.
Day 7 study questionnaire 1	Day 7 (Pages 11-12)	Please fill in both these questionnaires on day 7.
Day 7 study questionnaire 2	Day 7 (Page 13)	
Potential side-effects of study medication	Day 7 (Page 14)	If you like, please feel free to note things down in these sections as they happen through the week. Please check on day 7 that you have written down everything you want to tell us.
Daily activities and childcare	Day 7 (Page 15)	
Health service contacts	Day 7 (Page 16)	

If you have any questions, please see our website (www.archiestudy.com) or get in touch with us by phone (01865 617842) or e-mail (archie@phc.ox.ac.uk).

Day 1

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Your Child's Study Medication

Morning dose given? (please tick ONE answer)	Yes: ☐ No: ☐
Evening dose given? (please tick ONE answer)	Yes: ☐ No: ☐

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 14
- Daily activities and childcare, page 15
- Health Service Contacts, page 16

Day 2

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Your Child's Study Medication

Morning dose given? (please tick ONE answer)	Yes: ☐	No: ☐
Evening dose given? (please tick ONE answer)	Yes: ☐	No: ☐

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or a complication of this? (Please tick)

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (please circle)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 14
- Daily activities and childcare, page 15
- Health Service Contacts, page 16

Day 3

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Your Child's Study Medication

Morning dose given? (please tick ONE answer)	Yes: ☐	No: ☐
Evening dose given? (please tick ONE answer)	Yes: ☐	No: ☐

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or a complication of this? (Please tick)

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (please circle)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 14
- Daily activities and childcare, page 15
- Health Service Contacts, page 16

Day 4

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	1	2	3	4	5	6
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Your Child's Study Medication

Morning dose given? (please tick ONE answer)	Yes: ☐	No: ☐
Evening dose given? (please tick ONE answer)	Yes: ☐	No: ☐

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or a complication of this? (Please tick)

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (please circle)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

Now please fill in your day 4 Study Questionnaire on pages 6 and 7

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 14
- Daily activities and childcare, page 15
- Health Service Contacts, page 16

Day 4 Study Questionnaire

Describing the child's health today

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think **the child** would mark to describe his/her own health **TODAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she has no problems walking about ❑
He/she has some problems walking about ❑
He/she has a lot of problems walking about ❑

Looking after myself

He/she has no problems washing or dressing him/herself ❑
He/she has some problems washing or dressing him/herself ❑
He/she has a lot of problems washing or dressing him/herself ❑

Doing usual activities (for example. *going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑
He/she has some problems doing his/her usual activities ❑
He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑
He/she has some pain or discomfort ❑
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy ❑
He/she is a bit worried, sad or unhappy ❑
He/she is very worried, sad or unhappy ❑

How good is the health of the child TODAY

- We would like to know how good or bad you think **the child** would rate **his/her** own health TODAY

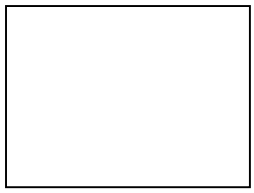
- This line is numbered from 0 to 100

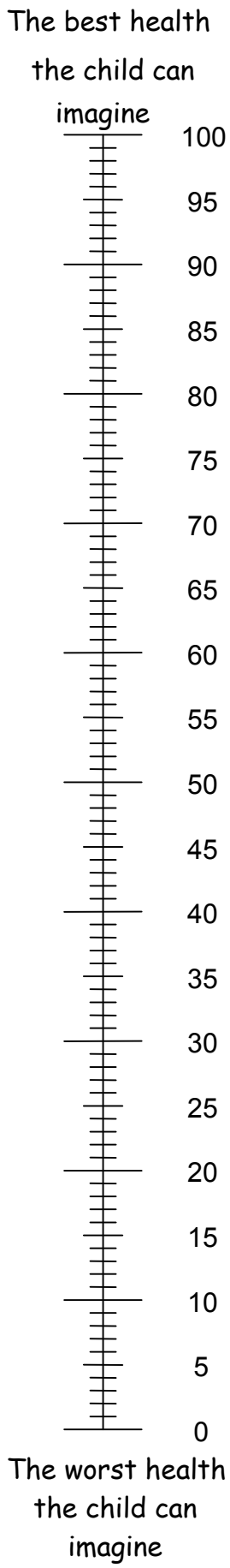
- 100 means the best health the child can imagine

  0 means the worst health the child can imagine

Please, mark an X on the line that shows how good or bad you think **the child** would rate **his/her** health TODAY

Now, please write the number you marked on the scale in the box below.





Day 5

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Your Child's Study Medication

Morning dose given? (please tick ONE answer)	Yes: ☐	No: ☐
Evening dose given? (please tick ONE answer)	Yes: ☐	No: ☐

Other Medication for your Child flu-like illness

Today have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications)?

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (please circle)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 14
- Daily activities and childcare, page 15
- Health Service Contacts, page 16

Day 6

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	1	2	3	4	5	6
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Your Child's Study Medication

If you have already given your child 10 doses of study medication please DO NOT give any further doses. Please discard any leftover medication.

Morning dose given? (please tick ONE answer)	Yes: ☐ No: ☐
Evening dose given? (please tick ONE answer)	Yes: ☐ No: ☐

Other Medication for your Child flu-like illness

Today have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications)?

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (please circle)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 14
- Daily activities and childcare, page 15
- Health Service Contacts, page 16

Day 7

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	**SCORE**						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Your Child's Study Medication

You will have most likely finished giving your child all 10 doses of study medication. Please discard any unused study medication.

Other Medication for your Child flu-like illness

Today have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications)?

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (please circle)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

Now please fill in your day 7 Study Questionnaire 1 (pages 11 and 12) and day 7 Study Questionnaire 2 (page 13)

Please also remember to tell us about:

- Potential side-effects of study medication, page 14
- Daily activities and childcare, page 15
- Health Service Contacts, page 16

Day 7 Study Questionnaire 1

Describing the child's health today

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think **the child** would mark to describe his/her own health **TODAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she has no problems walking about ❑
He/she has some problems walking about ❑
He/she has a lot of problems walking about ❑

Looking after myself

He/she has no problems washing or dressing him/herself ❑
He/she has some problems washing or dressing him/herself ❑
He/she has a lot of problems washing or dressing him/herself ❑

Doing usual activities (for example. *going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑
He/she has some problems doing his/her usual activities ❑
He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑
He/she has some pain or discomfort ❑
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy ❑
He/she is a bit worried, sad or unhappy ❑
He/she is very worried, sad or unhappy ❑

How good is the health of the child TODAY

- We would like to know how good or bad you think **the child** would rate **his/her** own health TODAY

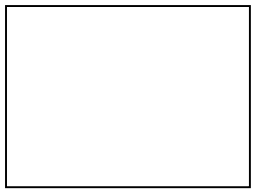
- This line is numbered from 0 to 100

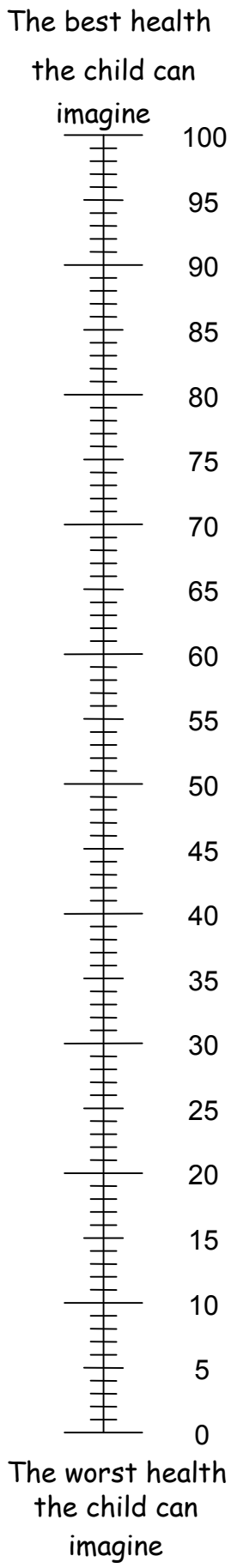
- 100 means the best health the child can imagine

  0 means the worst health the child can imagine

Please, mark an X on the line that shows how good or bad you think **the child** would rate **his/her** health TODAY

Now, please write the number you marked on the scale in the box below.





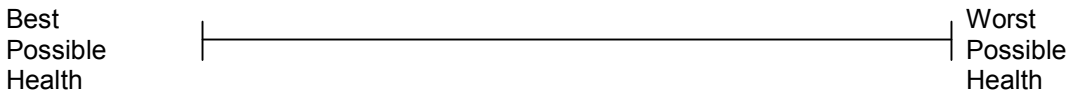
Day 7 Study Questionnaire 2

How much of a problem have the following symptoms been for your child today?

Please tick ONE box for each symptom.

	Symptom	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know or Not Applicable
1	Poor appetite					
2	Not sleeping well					
3	Irritable, cranky, fussy					
4	Feels unwell					
5	Low energy tired					
6	Not playing well					
7	Crying more than usual					
8	Needing extra care					
9	Clinginess					
10	Headache					
11	Sore throat					
12	Muscle aches and pains					
13	Fever					
14	Cough					
15	Nasal congestion, runny nose					
16	Vomiting					
17	Not interested in what's going on					
18	Unable to get out of bed					

Please mark on this line how sick your child is today:



POTENTIAL SIDE-EFFECTS OF STUDY MEDICATION (please complete on day 7)

1. **Has your child had diarrhoea in the last week?**

   Yes: ☐ No: ☐

2. **Has your child been feeling sick or been sick in the last week?**

   Yes: ☐ No: ☐

3. **Has your child had a skin rash in the last week?**

   Yes: ☐ No: ☐

4. **Has your child had thrush in the last week?**

   Yes: ☐ No: ☐

5. **Has your child had other side-effects from the study medication in the last week?**

   Yes: ☐ No: ☐ If yes, please provide details below:

_____

_____

_____

DAILY ACTIVITIES AND CHILDCARE
(Please complete on day 7)

For each of the following questions, please enter the number of days in the space provided. Please enter '0' if your answer is 'no days'. Please circle 'not applicable' if the question does not apply to you or your child.

Due to your child's flu-like illness or complications of this:

1. How many days in the past week was your child unable to attend school or nursery?

   _____ days / not applicable

2. If you are in paid employment, how many days in the past week have you been unable to attend work?

   _____days / not applicable

3. If you are not in paid employment, how many days in the past week have you changed your usual activities?

   _____days / not applicable

4. How many days in the past week was an outside carer required?

   _____days / not applicable

HEALTH SERVICE CONTACTS

During the past week, has your child had to spend one or more nights in hospital because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Date your child went into hospital	Date your child was discharged from hospital	Reason why your child had to stay in hospital

During the past week, has your child come into contact with any of the following because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Family doctor (GP) visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Practice nurse visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Hospital visits	
Accident and Emergency department	Outpatient department
Date:	Date:
Date:	Date:
Date:	Date:

Other visits (please specify):		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Telephone calls			
Family doctor (GP)	Practice nurse	Other	
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:

Thank you for filling in this diary for your child.

Return options:

- Email to archie@phc.ox.ac.uk.
  Please remember to include your child's Archie ID number in the subject line.

- Post
  Please use the freepost envelope provided.

The early use of

Antibiotics in 'at Risk' CHildren with InfluEnza

Study Diary – Week 2

Archie ID: _____

To be completed by healthcare professional:

Day of study entry (day 1): Day of week_____Date (dd/mm/yyyy)_____

Key days to remember for filling in this diary:

Day 14	Day of week_____Date (dd/mm/yyyy)_____

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WEEK 2 DIARY CONTENTS

Thank you for agreeing to fill in this diary for your child. Please try to fill it in at the end of each day. Please complete as much information as you can, but don't worry if you miss something by mistake – just keep going!

Contents	When should I fill this in?	Should I fill this in if my child is feeling better?	Tips and advice
Your child's symptoms	Days 8 to 14	No, you can stop once your child has scored '0' for every symptom for two days in a row.	
Your child's temperature	Days 8 to 14	No, you can stop once it has been 37.4 degrees or below for two days in a row.	Please take your child's temperature at bedtime OR before giving medicine to lower his/her temperature (*e.g.* paracetamol, ibuprofen), whichever happens first.
Other medication for your child's flu-like illness	Days 8 to 14 (if applicable)	Yes	Please write down any additional medicines you give for his/her flu-like illness or any complications of this. This includes higher doses of usual medications.
Day 14 study questionnaire	Day 14 (Pages 9 -10)	Yes	Please fill this in on day 14.
Potential side-effects from study medication	Day 14 (Page 11)	Yes	If you like, please feel free to note things down in these sections as they happen through the week. Please check on day 14 that you have written down everything you want to tell us.
Daily activities and childcare	Day 14 (Page 12)	Yes	
Health service contacts	Day 14 (Page 13)	Yes	

Day 8

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 11
- Daily activities and childcare, page 12
- Health Service Contacts, page 13

Day 9

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 11
- Daily activities and childcare, page 12
- Health Service Contacts, page 13

Day 10

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 11
- Daily activities and childcare, page 12
- Health Service Contacts, page 13

Day 11

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 11
- Daily activities and childcare, page 12
- Health Service Contacts, page 13

Day 12

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 11
- Daily activities and childcare, page 12
- Health Service Contacts, page 13

Day 13

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Potential side-effects of study medication, page 11
- Daily activities and childcare, page 12
- Health Service Contacts, page 13

Day 14

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

Now please fill in your day 14 Study Questionnaire (pages 9 and 10)

Please also remember to tell us about:

- Potential side-effects of study medication, page 11
- Daily activities and childcare, page 12
- Health Service Contacts, page 13

Day 14 Study Questionnaire

Describing the child's health today

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think **the child** would mark to describe his/her own health **TODAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she has no problems walking about ❑
He/she has some problems walking about ❑
He/she has a lot of problems walking about ❑

Looking after myself

He/she has no problems washing or dressing him/herself ❑
He/she has some problems washing or dressing him/herself ❑
He/she has a lot of problems washing or dressing him/herself ❑

Doing usual activities (for example. *going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑
He/she has some problems doing his/her usual activities ❑
He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑
He/she has some pain or discomfort ❑
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy ❑
He/she is a bit worried, sad or unhappy ❑
He/she is very worried, sad or unhappy ❑

How good is the health of the child TODAY

- We would like to know how good or bad you think **the child** would rate **his/her** own health TODAY

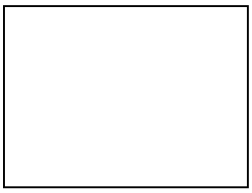
- This line is numbered from 0 to 100

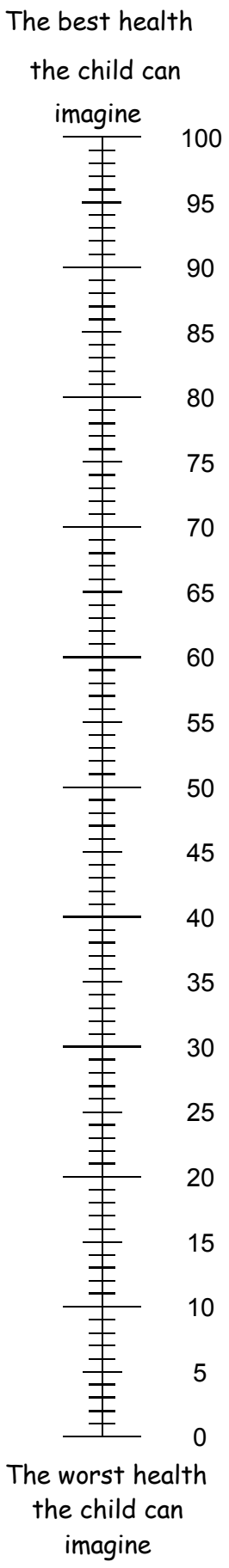
- 100 means the best health the child can imagine

  0 means the worst health the child can imagine

Please, mark an X on the line that shows how good or bad you think **the child** would rate **his/her** health TODAY

Now, please write the number you marked on the scale in the box below.





POTENTIAL SIDE-EFFECTS OF STUDY MEDICATION (please complete on day 14)

1. **Has your child had diarrhoea in the last week?**
   Yes: ☐ No: ☐

2. **Has your child been feeling sick or been sick in the last week?**
   Yes: ☐ No: ☐

3. **Has your child had a skin rash in the last week?**
   Yes: ☐ No: ☐

4. **Has your child had thrush in the last week?**
   Yes: ☐ No: ☐

5. **Has your child had other side-effects from the study medication in the last week?**
   Yes: ☐ No: ☐ If yes, please provide details below:

_____

_____

_____

DAILY ACTIVITIES AND CHILDCARE
(Please complete on day 14)

For each of the following questions, please enter the number of days in the space provided. Please enter '0' if your answer is 'no days'. Please circle 'not applicable' if the question does not apply to you or your child.

Due to your child's flu-like illness or complications of this:

1. How many days in the past week was your child unable to attend school or nursery?

   _____ days / not applicable

2. If you are in paid employment, how many days in the past week have you been unable to attend work?

   _____days / not applicable

3. If you are not in paid employment, how many days in the past week have you changed your usual activities?

   _____days / not applicable

4. How many days in the past week was an outside carer required?

   _____days / not applicable

HEALTH SERVICE CONTACTS

During the past week, has your child had to spend one or more nights in hospital because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Date your child went into hospital	Date your child was discharged from hospital	Reason why your child had to stay in hospital

During the past week, has your child come into contact with any of the following because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Family doctor (GP) visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Practice nurse visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Hospital visits	
Accident and Emergency department	Outpatient department
Date:	Date:
Date:	Date:
Date:	Date:

Other visits (please specify):		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Telephone calls			
Family doctor (GP)	Practice nurse	Other	
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:

Thank you for filling in this diary for your child.

Return options:

- Email to archie@phc.ox.ac.uk.
  Please remember to include your child's Archie ID number in the subject line.

- Post
  Please use the freepost envelope provided.

The early use of

Antibiotics in 'at Risk' CHildren with InfluEnza

Study Diary – Week 3

Archie ID: _____

To be completed by healthcare professional:

Day of study entry (day 1): Day of week_____Date (dd/mm/yyyy)_____

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WEEK 3 DIARY CONTENTS

Thank you for agreeing to fill in this diary for your child. Please try to fill it in at the end of each day. Please complete as much information as you can, but don't worry if you miss something by mistake – just keep going!

Contents	When should I fill this in?	Should I fill this in if my child is feeling better?	Tips and advice
Your child's symptoms	Days 15 to 21	No, you can stop once your child has scored '0' for every symptom for two days in a row.	
Your child's temperature	Days 15 to 21	No, you can stop once it has been 37.4 degrees or below for two days in a row.	Please take your child's temperature at bedtime OR before giving medicine to lower his/her temperature (*e.g.* paracetamol, ibuprofen), whichever happens first.
Other medication for your child's flu-like illness	Days 15 to 21 (if applicable)	Yes	Please write down any additional medicines you give for his/her flu-like illness or any complications of this. This includes higher doses of usual medications.
Daily activities and childcare	Day 21 (Page 9)	Yes	If you like, please feel free to note things down in these sections as they happen through the week. Please check on day 21 that you have written down everything you want to tell us.
Health service contacts	Day 21 (Page10)	Yes	

Day 15

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 9
- Health Service Contacts, page 10

Day 16

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 9
- Health Service Contacts, page 10

Day 17

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 9
- Health Service Contacts, page 10

Day 18

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 9
- Health Service Contacts, page 10

Day 19

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 9
- Health Service Contacts, page 10

Day 20

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 9
- Health Service Contacts, page 10

Day 21

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

Now please remember to tell us about:

- Daily activities and childcare, page 9
- Health Service Contacts, page 10

DAILY ACTIVITIES AND CHILDCARE
(Please complete on day 21)

For each of the following questions, please enter the number of days in the space provided. Please enter '0' if your answer is 'no days'. Please circle 'not applicable' if the question does not apply to you or your child.

Due to your child's flu-like illness or complications of this:

1. How many days in the past week was your child unable to attend school or nursery?

   _____ days / not applicable

2. If you are in paid employment, how many days in the past week have you been unable to attend work?

   _____days / not applicable

3. If you are not in paid employment, how many days in the past week have you changed your usual activities?

   _____days / not applicable

4. How many days in the past week was an outside carer required?

   _____days / not applicable

HEALTH SERVICE CONTACTS

During the past week, has your child had to spend one or more nights in hospital because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Date your child went into hospital	Date your child was discharged from hospital	Reason why your child had to stay in hospital

During the past week, has your child come into contact with any of the following because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Family doctor (GP) visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Practice nurse visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Hospital visits	
Accident and Emergency department	Outpatient department
Date:	Date:
Date:	Date:
Date:	Date:

Other visits (please specify):		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Telephone calls			
Family doctor (GP)	Practice nurse	Other	
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:

Thank you for filling in this diary for your child.

Return options:

- Email to archie@phc.ox.ac.uk.
  Please remember to include your child's Archie ID number in the subject line.

- Post
  Please use the freepost envelope provided.

The early use of

Antibiotics in 'at Risk' CHildren with InfluEnza

Study Diary – Week 4

Archie ID: _____

To be completed by healthcare professional:

Day of study entry (day 1): Day of week_____Date (dd/mm/yyyy)_____

Key days to remember for filling in this diary:

Day 28	Day of week_____Date (dd/mm/yyyy)_____

UNIVERSITY OF OXFORD

WEEK 4 DIARY CONTENTS

Thank you for agreeing to fill in this diary for your child. Please try to fill it in at the end of each day. Please complete as much information as you can, but don't worry if you miss something by mistake – just keep going!

Contents	When should I fill this in?	Should I fill this in if my child is feeling better?	Tips and advice
Your child's symptoms	Days 22 to 28	No, you can stop once your child has scored '0' for every symptom for two days in a row.	
Your child's temperature	Days 22 to 28	No, you can stop once it has been 37.4 degrees or below for two days in a row.	Please take your child's temperature at bedtime OR before giving medicine to lower his/her temperature (*e.g.* paracetamol, ibuprofen), whichever happens first.
Other medication for your child's flu-like illness	Days 22 to 28 (if applicable)	Yes	Please write down any additional medicines you give for his/her flu-like illness or any complications of this. This includes higher doses of usual medications.
Day 28study questionnaire	Day 28 (Pages 9 -10)	Yes	Please fill this in on day 28.
Daily activities and childcare	Day 28 (Page 11)	Yes	If you like, please feel free to note things down in these sections as they happen through the week. Please check on day 28 that you have written down everything you want to tell us.
Health service contacts	Day 28 (Page 12)	Yes	

ARCHIE Diary wk4, 12Mar14v.1.1
REC 13/NW/0621

Day 22

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 11
- Health Service Contacts, page 12

Day 23

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 11
- Health Service Contacts, page 12

Day 24

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 11
- Health Service Contacts, page 12

Day 25

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 11
- Health Service Contacts, page 12

Day 26

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 11
- Health Service Contacts, page 12

Day 27

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

Symptoms	SCORE						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

At the end of this week please remember to tell us about:

- Daily activities and childcare, page 11
- Health Service Contacts, page 12

Day 28

Your Child's Symptoms

How much of a problem have the following symptoms been for your child today?
Please tick ONE score for each symptom.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	**SCORE**						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Cough							
Phlegm							
Shortness of breath							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities							

Your Child's Temperature

Please write down your child's temperature as it appears on the thermometer display (*e.g.* 37.8)	°C
Please write down the time you took your child's temperature today (*e.g.* 8:30 ~~am~~/pm)	____:____ am/pm (*delete as appropriate*)

Other medication for your child's flu-like illness

Thinking about today, have you given your child any over the counter (OTC) or prescribed medicines (including higher doses of your child's usual medications) for his/her flu-like illness or any complications of this? **Please tick ONE answer.**

Yes: ☐ No: ☐ If yes, please use the table below to provide details

Name of medicine	Number of doses	OTC or prescribed? (*delete as appropriate*)
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed
		OTC / prescribed

Now please fill in your day 28 Study Questionnaire (pages 9 and 10)

Please also remember to tell us about:

- Daily activities and childcare, page 11
- Health Service Contacts, page 12

Day 28 Study Questionnaire

Describing the child's health today

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think **the child** would mark to describe his/her own health **TODAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she has no problems walking about ❑
He/she has some problems walking about ❑
He/she has a lot of problems walking about ❑

Looking after myself

He/she has no problems washing or dressing him/herself ❑
He/she has some problems washing or dressing him/herself ❑
He/she has a lot of problems washing or dressing him/herself ❑

Doing usual activities (for example. *going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑
He/she has some problems doing his/her usual activities ❑
He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑
He/she has some pain or discomfort ❑
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy ❑
He/she is a bit worried, sad or unhappy ❑
He/she is very worried, sad or unhappy ❑

How good is the health of the child TODAY

- We would like to know how good or bad you think **the child** would rate **his/her** own health TODAY

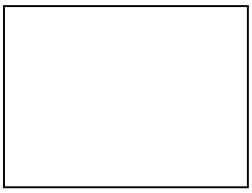
- This line is numbered from 0 to 100

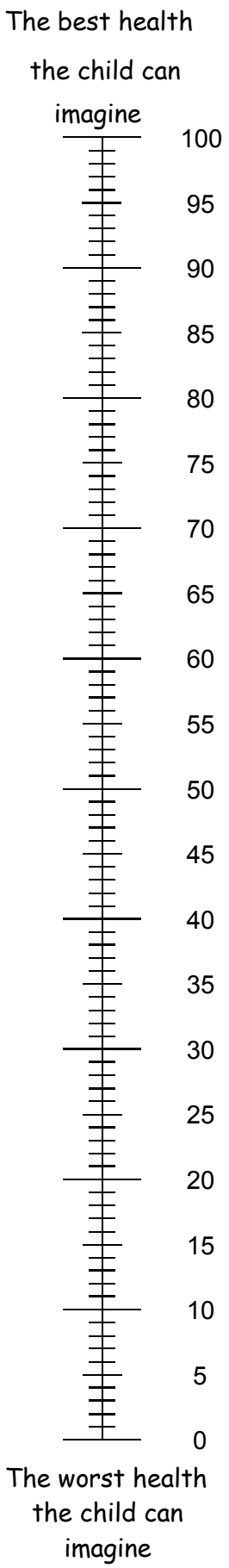
- 100 means the best health the child can imagine

  0 means the worst health the child can imagine

Please, mark an X on the line that shows how good or bad you think **the child** would rate **his/her** health TODAY

Now, please write the number you marked on the scale in the box below.





DAILY ACTIVITIES AND CHILDCARE
(Please complete on day 28)

For each of the following questions, please enter the number of days in the space provided. Please enter '0' if your answer is 'no days'. Please circle 'not applicable' if the question does not apply to you or your child.

Due to your child's flu-like illness or complications of this:

1. How many days in the past week was your child unable to attend school or nursery?

   _____ days / not applicable

2. If you are in paid employment, how many days in the past week have you been unable to attend work?

   _____days / not applicable

3. If you are not in paid employment, how many days in the past week have you changed your usual activities?

   _____days / not applicable

4. How many days in the past week was an outside carer required?

   _____days / not applicable

HEALTH SERVICE CONTACTS

During the past week, has your child had to spend one or more nights in hospital because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Date your child went into hospital	Date your child was discharged from hospital	Reason why your child had to stay in hospital

During the past week, has your child come into contact with any of the following because of his/her flu-like illness or complications of this?

Yes: ☐ No: ☐ If YES, please give us further details in the table below:

Family doctor (GP) visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Practice nurse visits		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Hospital visits	
Accident and Emergency department	Outpatient department
Date:	Date:
Date:	Date:
Date:	Date:

Other visits (please specify):		
Working hours	Out of hours	Home visits
Date:	Date:	Date:
Date:	Date:	Date:
Date:	Date:	Date:

Telephone calls			
Family doctor (GP)	Practice nurse	Other	
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:
Date:	Date:	Date:	With whom:

Thank you for filling in this final diary for your child.

Return options:

- Email to archie@phc.ox.ac.uk.
  Please remember to include your child's Archie ID number in the subject line.

- Post
  Please use the freepost envelope provided.

ARCHIE

The early use of Antibiotics in at Risk Children with InfluEnza

__ __ __ / __ __ __ __

ARCHIE ID

WEEK 1 FOLLOW-UP

Questions for participant's parent/guardian - to be completed by healthcare professional or research assistant at week 1 telephone consultation (can be done from day 7 to day 10 inclusive).

Date of study entry (day 1) | D | D | M | M | Y | Y | Y | Y |

Date of week 1 follow-up | D | D | M | M | Y | Y | Y | Y |

During the last week:

1. Have you and your child had to seek medical advice because of your child's flu-like illness or complications of this (*e.g.* chest infection, ear infection)? **YES** ☐ **NO** ☐
   *If **YES**, please remember to note these occasions in your ARCHIE study diary.*

2. Has your child had to stay in hospital for one or more nights because of his or her flu-like illness or complications of this (*e.g.* chest infection, ear infection)? **YES** ☐ **NO** ☐
   *If **YES**, please remember to note these occasions in your ARCHIE study diary.*

3. Has your child had any side-effects from his or her study medication? **YES** ☐ **NO** ☐
   *If **YES**, please give details below.*

Please tick all side-effects that apply:

☐ Diarrhoea ☐ Nausea (feeling sick) ☐ Vomiting (being sick) ☐ Thrush (fungal infection of mouth, vagina or skin folds)	☐ Skin rash ☐ Other(s) (please state below)
N.B. ACTION if any of the above are ticked	**N.B. ACTION if any of the above are ticked**
ACTION: Complete an **Adverse Event Report form** for **each clinically severe** side-effect. No action is required for clinically mild or moderate side-effects.	**ACTION:** Complete an **Adverse Event Report form** for **each** side-effect, regardless of clinical severity.
Complete a **Serious Adverse Event Report form** for **ANY side-effect** which has **serious consequences.** See Serious Adverse Event Report form in section 6 for full definition.	

You will find Adverse Event and Serious Adverse Event report forms in section 6 of your study pack or on our website (www.archiestudy.com).

4. ***For parents/guardians who did NOT agree to point 8 on the consent form at study entry:***
   To help us work out whether antibiotics might be helpful if your child gets similar infections in the future, would you be happy for us to take follow-up throat swabs from your child after 3 months, 6 months and 12 months? **YES** ☐ **NO** ☐ **NOT APPLICABLE (already agreed)** ☐

Please remind parent/guardian to return completed week 1 study diary by e-mail (with ARCHIE ID in subject line) or post.

ARCHIE

The early use of Antibiotics in at Risk Children with InfluEnza

__ __ __ /__ __ __ __

ARCHIE ID

WEEK 2 FOLLOW-UP

Questions for participant's parent/guardian - to be completed by healthcare professional or research assistant at week 2 telephone consultation (can be done from day 14 to day 17 inclusive).

Date of study entry (day 1) | D | D | M | M | Y | Y | Y | Y |

Date of week 2 follow-up | D | D | M | M | Y | Y | Y | Y |

Did they return the week 1 diary? **Yes, by email** ☐ **Yes, by post** ☐ **No** ☐

During the last week:

1. Have you and your child had to seek medical advice because of your child's flu-like illness or complications of this (*e.g.* chest infection, ear infection)? **YES** ☐ **NO** ☐
   *If **YES**, please remember to note these occasions in your ARCHIE study diary.*

2. Has your child had to stay in hospital for one or more nights because of his or her flu-like illness or complications of this (*e.g.* chest infection, ear infection)? **YES** ☐ **NO** ☐
   *If **YES**, please remember to note these occasions in your ARCHIE study diary.*

3. Has your child had any side-effects from his or her study medication? **YES** ☐ **NO** ☐
   *If **YES**, please give details below.*

Please tick all side-effects that apply:

☐ Diarrhoea ☐ Nausea (feeling sick) ☐ Vomiting (being sick) ☐ Thrush (fungal infection of mouth, vagina or skin folds)	☐ Skin rash ☐ Other(s) (please state below)
N.B. ACTION if any of the above are ticked	**N.B. ACTION if any of the above are ticked**
ACTION: Complete an **Adverse Event Report form** for **each clinically severe** side-effect. No action is required for clinically mild or moderate side-effects.	**ACTION:** Complete an **Adverse Event Report form** for **each** side-effect, regardless of clinical severity.

Complete a **Serious Adverse Event Report form** for **ANY side-effect** which has **serious consequences.** See Serious Adverse Event Report form in section 6 for full definition.

You will find Adverse Event and Serious Adverse Event report forms in section 6 of your study pack or on our website (www.archiestudy.com).

4. ***For parents/guardians who have not previously agreed to follow-up throat swabs (check consent form point 8 and week 1 follow-up form point 4):***
   To help us work out whether antibiotics might be helpful if your child gets similar infections in the future, would you be happy for us to take follow-up throat swabs from your child after 3 months, 6 months and 12 months?
   YES ☐ **NO** ☐
   NOT APPLICABLE (already agreed) ☐

Please remind parent/guardian to return completed week 2 study diary by e-mail (with ARCHIE ID in subject line) or post.

Site ID
ARCHIE ID

ARCHIE MEDICAL NOTES REVIEW

To be completed for ALL ARCHIE trial participants

The information needed to complete this notes review form can be extracted from specific sections of the medical record as detailed below.

Notes review sections	Section of medical record needed
Re-consultations, days 1 to 28 inclusive Interventions, days 1 to 28 inclusive Hospital admissions, days 1 to 28 inclusive Death during period from days 1 to 28 inclusive	Acute consultations in GP surgery, discharge summaries from out of hours primary care centres, walk-in centres, Accident and Emergency and hospital relating to period from day 1 to day 28 inclusive.
Participant's medical history	Active problems Repeat medications Immunisations Acute consultations in GP surgery relating to period during 12 month period before study entry. Past medications from 3 months before study entry to day 28.

Information for research assistants

- To complete this notes review, you may ask the participant's GP surgery to send printouts of the above sections. Printouts should be labelled with the participant's ARCHIE ID number and patient identifiable information should be removed.
- If you are completing the notes review by telephone, please complete the baseline information below before contacting the participant's GP surgery.

BASELINE INFORMATION

Date of study entry (day 1) | D | D | M | M | Y | Y | Y | Y |

Date of day 28 | D | D | M | M | Y | Y | Y | Y |

Follow-up throat swabs

Consent given by parent/guardian for follow-up throat swabs? YES ☐ NO ☐

If **YES**, please remember to do an **ADDITIONAL ARCHIE NOTES REVIEW** for this participant after his/her last follow-up throat swab has been taken.

Site ID
ARCHIE ID

RE-CONSULTATIONS, days 1 to 28 inclusive **YES** ☐ **NO** ☐ If **YES**, give details below:

Definition of 're-consultations': *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. Re-consultations do NOT include routine chronic disease monitoring visits, planned visits advised by a healthcare professional or visits done as part of a research study.*

RE-CONSULTATION EPISODE:	**1**	**2**	**3**	**4**
Date (dd/mm/yyyy)				
Same illness episode for which child was recruited into ARCHIE?	☐ YES ☐ NO ☐ UNCLEAR	☐ YES ☐ NO ☐ UNCLEAR	☐ YES ☐ NO ☐ UNCLEAR	☐ YES ☐ NO ☐ UNCLEAR
IF YES, give reason (tick ONE box)				
Same symptoms as original consultation and documented worsening	☐	☐	☐	☐
Same symptoms as original consultation but not clearly worsening	☐	☐	☐	☐
No further information on symptoms from original consultation	☐	☐	☐	☐
New symptoms? **(If YES, tick all that apply)**	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Runny nose/blocked nose/rhinorrhoea/coryza/nasal congestion				
Sore throat/difficult or painful swallowing/inflamed pharynx or tonsils				
Earache/ear pain/otalgia/difficulty hearing/ ear discharge/red ear				
Sinus pain/tenderness				
Sputum/phlegm				
Chest/shoulder pain				
Wheeze				
Dyspnoea/short of breath/difficulty in breathing				
Other (please state)				
New diagnoses? **(If YES, tick all that apply)**	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Sinusitis				
Tonsillitis/pharyngitis/throat abscess/quinsy/peritonsillar cellulitis				
Pneumonia/chest infection/lower respiratory tract infection/bronchitis				
Exacerbation of asthma/viral wheeze				
Otitis media/ear infection				
Other (please state)				

Site ID
ARCHIE ID

INTERVENTIONS, days 1 to 28 inclusive

RE-CONSULTATION EPISODE:	**1**	**2**	**3**	**4**
Date (dd/mm/yyyy): see previous page				
Any medications, investigations or referral to hospital? If **YES**, give further details below:	☐ YES ☐ NO ☐ UNCLEAR	☐ YES ☐ NO ☐ UNCLEAR	☐ YES ☐ NO ☐ UNCLEAR	☐ YES ☐ NO ☐ UNCLEAR
Antibiotics given? If YES, please specify below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Generic name				
Dose				
Number of doses per day				
Duration (days)				
Other treatments given? If YES, please specify below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Generic name (drug 1)				
Dose				
Number of doses per day				
Duration (days)				
Generic name (drug 2)				
Dose				
Number of doses per day				
Duration (days)				
Generic name (drug 3)				
Dose				
Number of doses per day				
Duration (days)				
Investigations requested? If YES please specify below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Chest X ray If YES, specify date and result	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Date chest X ray performed (dd/mm/yyyy)				
Result of chest X ray				
Other investigations If YES, please give details below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Type of other investigation 1				
Date performed (dd/mm/yyyy)				
Result				
Type of other investigation 2	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Date performed (dd/mm/yyyy)				
Result				
Referral to hospital team/A+E for acute admission?	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO

Site ID
ARCHIE ID

HOSPITAL ADMISSIONS, days 1 to 28 inclusive

Has the participant had any acute hospital admission episodes, when he or she has had to spend **one or more nights in hospital**? **YES** ☐ **NO** ☐ If **YES**, give details below:

ADMISSION EPISODE:	**1**	**2**	**3**	**4**
Date admitted (dd/mm/yyyy)				
Date discharged (dd/mm/yyyy)				
Antibiotics given? If YES, please specify below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Generic name				
Dose				
Number of doses per day				
Route of administration				
Duration (days)				
Other treatments given? If YES, please specify below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Generic name (drug 1)				
Dose				
Number of doses per day				
Route of administration				
Duration (days)				
Generic name (drug 2)				
Dose				
Number of doses per day				
Route of administration				
Duration (days)				
Generic name (drug 3)				
Dose				
Number of doses per day				
Route of administration				
Duration (days)				
Investigations requested? If YES please specify below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Chest X ray If YES, specify date and result	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Date chest X ray performed (dd/mm/yyyy)				
Result of chest X ray				
Other investigation If YES, please give details below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Type of other investigation				
Date performed (dd/mm/yyyy)				
Result				
Admitted to Intensive Care Unit? If YES, please give details below	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Date admitted to Intensive Care Unit (dd/mm/yyyy)				
Date discharged from Intensive Care Unit (dd/mm/yyyy)				

DEATH during period from days 1 to 28 inclusive

Death? **If YES, please give details below**	☐ YES ☐ NO
Date of death (dd/mm/yyyy)	
Reason for death	

If hospital admission or death has occurred and has not been reported as a Serious Adverse Event, please report this within 24 hours of becoming aware of the event using a Serious Adverse Event report form.

PARTICIPANT'S MEDICAL HISTORY

'AT RISK' MEDICAL PROBLEM – please tick all boxes that apply:

☐ Asthma	☐ Bronchopulmonary dysplasia
☐ Recurrent viral wheeze (3 or more episodes within last 12 months	☐ Admitted to hospital with bronchiolitis within last 12 months
☐ Congenital heart disease	☐ Chronic heart failure
☐ Cerebral palsy	☐ Other neurological or neuromuscular disorder. Please specify:_____
☐ Chronic kidney disease	☐ Nephrotic syndrome
☐ Kidney transplantation	☐ Liver disease Please specify:_____
☐ Asplenia or splenic dysfunction	☐ HIV infection
☐ Chemotherapy leading to immunosuppression	☐ Systemic steroids (prednisolone 20 mg or more a day or >=1 mg/kg/day (children under 20 kg)
☐ Type 1 diabetes mellitus	☐ Type 2 diabetes mellitus
☐ Down's syndrome	☐ Other genetic abnormality. Please specify: _____
☐ Sickle cell disease	☐ Malignancy Please specify: _____
☐ Prematurity (born before 37 weeks gestation and aged 6 to 23 months at time of study entry)	☐ Other Please specify:_____

REGULAR MEDICATIONS AT TIME OF STUDY ENTRY **YES** ☐ **NO** ☐

If **YES**, please give details in table below:

Generic name	Dose	Number of doses per day

VACCINATIONS

Type	Recorded?	Dose 1 (dd/mm/yy)	Dose 2 (dd/mm/yy)	Dose 3 (dd/mm/yy)	Dose 4 (dd/mm/yy)	Dose 5 (dd/mm/yy)
Hib	☐ YES ☐ NO					
PCV	☐ YES ☐ NO If YES, state type: ☐ PCV7 ☐ PCV 13 ☐ Unknown					
Seasonal flu (SAME season as when child recruited)	☐ YES ☐ NO					
Seasonal flu (season BEFORE child recruited)	☐ YES ☐ NO					
Pandemic flu	☐ YES ☐ NO					

Site ID
ARCHIE ID

ACUTE CONSULTATIONS DURING 12-MONTH PERIOD BEFORE STUDY ENTRY YES ☐ NO ☐

If YES, give details below:

Definition of 'acute consultations': *acute consultations are unplanned consultations in a GP surgery, out-of-hours primary care centre, primary care walk-in centre, child's home or Accident and Emergency department. Acute consultations do NOT include routine chronic disease monitoring visits, planned visits advised by a healthcare professional or visits done as part of a research study.*

Acute consultation episode	Date of consultation (dd/mm/yyyy)	Reason for consultation
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

SPACE FOR INFORMATION ABOUT ADDITIONAL ACUTE CONSULTATIONS DURING THE 12-MONTH PERIOD BEFORE STUDY ENTRY (if needed)

TOTAL NUMBER OF ACUTE CONSULTATIONS
DURING THE 12-MONTH PERIOD BEFORE STUDY ENTRY: ☐

Site ID
ARCHIE ID

ANTIBIOTICS GIVEN DURING 3-MONTH PERIOD BEFORE STUDY ENTRY **YES** ☐ **NO** ☐
(Do NOT record antibiotics given on day of study entry)

If **YES**, please give details below:

PENICILLIN **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Amoxicillin	☐ YES ☐ NO				
Ampicillin	☐ YES ☐ NO				
Penicillin V	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

PENICILLIN/BETA-LACTAMASE INHIBITOR **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Strength	Dose	Number of doses per day	Duration (days)
Co-amoxiclav	☐ YES ☐ NO					
Other (please write name below): _____	☐ YES ☐ NO					

Site ID
ARCHIE ID

CEPHALOSPORIN **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Cefalexin	☐ YES ☐ NO				
Cefradine	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

MACROLIDE **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Erythromycin	☐ YES ☐ NO				
Clarithromycin	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

QUINOLONE **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Moxifloxacin	☐ YES ☐ NO				
Ciprofloxacin	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

OTHER ANTIBIOTICS PRESCRIBED **YES** ☐ **NO** ☐

Generic name	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)

SPACE FOR ANY ADDITIONAL INFORMATION IF NEEDED

Page of notes review	Section of notes review	Additional information

Site ID
ARCHIE ID

ADDITIONAL ARCHIE NOTES REVIEW

To be completed for ARCHIE trial participants <u>who had one or more follow-up throat swabs</u>.

The information needed to complete this additional ARCHIE notes review can be extracted from the section of the participant's medical record on **past medications prescribed during period between date of study entry and date of last follow-up throat swab.**

Information for research assistants

- To complete this additional notes review, you may ask the participant's GP surgery to send a printout of the above section. Printouts should be labelled with the participant's ARCHIE ID number and patient identifiable information should be removed.
- If you are completing this additional notes review by telephone, please complete the baseline information below before contacting the participant's GP surgery.

BASELINE INFORMATION

Date of study entry (day 1) | *D* | *D* | *M* | *M* | *Y* | *Y* | *Y* | *Y* |

Dates of follow-up throat swabs

Timing of swab	Swab taken (please tick)?	Date swab taken (DD/MM/YYYY)
3 month	☐ YES ☐ NO	
6 month	☐ YES ☐ NO	
12 month	☐ YES ☐ NO	

Site ID
ARCHIE ID

ANTIBIOTICS GIVEN DURING 12-MONTH PERIOD AFTER STUDY ENTRY **YES** ☐ **NO** ☐
(Include antibiotics given on same day as study entry. Do NOT include study medication itself)

If **YES**, please give details below:

PENICILLIN **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Amoxicillin	☐ YES ☐ NO				
Ampicillin	☐ YES ☐ NO				
Penicillin V	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

PENICILLIN/BETA-LACTAMASE INHIBITOR **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Strength	Dose	Number of doses per day	Duration (days)
Co-amoxiclav	☐ YES ☐ NO					
Other (please write name below): _____	☐ YES ☐ NO					

Site ID
ARCHIE ID

CEPHALOSPORIN **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Cefalexin	☐ YES ☐ NO				
Cefradine	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

MACROLIDE **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Erythromycin	☐ YES ☐ NO				
Clarithromycin	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

QUINOLONE **YES** ☐ **NO** ☐

Generic name	Antibiotic prescribed?	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)
Moxifloxacin	☐ YES ☐ NO				
Ciprofloxacin	☐ YES ☐ NO				
Other (please write name below): _____	☐ YES ☐ NO				

Site ID
ARCHIE ID

OTHER ANTIBIOTICS PRESCRIBED **YES** ☐ **NO** ☐

Generic name	Date(s) prescribed (dd/mm/yyyy)	Dose	Number of doses per day	Duration (days)

SPACE FOR ANY ADDITIONAL INFORMATION IF NEEDED

Page of notes review	**Section of notes review**	**Additional information**

UNIVERSITY OF OXFORD

ARCHIE

The early use of Antibiotics in at Risk Children with InfluEnza

Primary Care Clinical Trials Unit

STUDY DISCONTINUATION FORM

ARCHIE ID:

Date of last scheduled visit participant attended:

d	d	m	m	2	0	y	y

PLEASE COMPLETE WITHDRAWAL SECTION OR LOSS TO FOLLOW UP SECTION AS APPLICABLE

WITHDRAWAL

Please indicate how the participant was withdrawn (tick one box) & specific reason if known

A. WITHDRAWAL BY RESPONSIBLE INVESTIGATOR	☐	**SPECIFIC REASON(S) FOR WITHDRAWAL:** ☐ Non adherence to study procedures ☐ Due to safety concerns ☐ Other Further Details: _____
B. WITHDRAWAL BY PARTICIPANT	☐	
C. WITHDRAWAL BY PARENT/GUARDIAN	☐	

Please indicate by ticking A, B, or C below:

☐ **A) The participant or their parent /guardian is willing to provide continued follow up and data collection subsequent to their withdrawal from the study as detailed below (tick all that apply):**

- ☐ **Follow up not requiring their involvement (*e.g.* Notes Review by research team);**
- ☐ **Follow up requiring their involvement (*e.g.* return of questionnaires/diaries).**

☐ B) The participant or their parent /guardian is not willing to provide continued follow up and data collection subsequent to their withdrawal from the study.

☐ C) The participant or their parent /guardian has indicated that they are not willing to allow use of any data, even prior to the point of withdrawal, for purposes of analysis.

OR

LOST TO FOLLOW-UP

The loss or lack of continuation of a subject to follow-up (categorisation as per Study Protocol) ☐

INSTRUCTIONS FOR RETURN: please use freepost reply envelope or email to ***archie@phc.ox.ac.uk***

Signature_____ Date_____

Primary Care Clinical Trials Unit

STANDARD OPERATING PROCEDURE
DM 09_01

Case Report Form (CRF): Completion and Correction

Issue Date:	Effective Date:	Review Date:
28/Nov/2011	05/Dec/2011	05/Dec/2013

Author:	Name Brendan Bradley	Title Clinical Data Manager
	Signature BBradley	Date 25 Nov 2011
Reviewer:	Name Christy Toms	Title Clinical Trial Manager
	Signature Christy Toms	Date 25/Nov/2011
Authoriser:	Name Andrew Farmer A Farmer	Title Director, PC - CTU
	Signature	Date 25 NOV 2011

1 INTRODUCTION AND SCOPE

This SOP describes the process for the management of data arising from Primary Care Clinical Trials Unit (PC-CTU) trials. Specifically it will describe the procedures for site based staff to follow when completing (and subsequently making corrections to) paper Case Report Forms (CRFs), for use in the capture of clinical trial data.

This SOP applies to trials where the PC-CTU is responsible for managing the trial.

2 ASSOCIATED DOCUMENTS

Case Report Form (CRF): Design, Development and Deployment SOP DM 02.

3 DEFINITIONS

Case Report Forms (CRFs) - A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

4 PROCEDURE

All CRFS should be completed (and if necessary corrected) in accordance with the ICH GCP guidelines, and should not contain any patient identifiable information. It is important when completing CRFs to ensure regulatory compliance.

4.1 Completing the CRF

CRFs should be completed according to the specifications of each study and only by those authorized to do so in the Delegation of Responsibility Log. Study specific CRF completion guidelines can be provided to site staff, or general instructions can be supplied within the Study Manual. The procedure for corrections and amendments must be given on the CRF or described in a document in the Trial Master File / Investigator Site File. The following points should be considered when capturing data onto CRFs -

- The CRF should be completed as soon as possible after each participant assessment
- Permanent ink should be used of a sufficient pressure to ensure copies are clear
- Blue or black ink should be used to allow for photocopying
- If the CRFs are printed on carbonless duplication paper (NCR paper) a suitable separator must be used under the form being completed, to prevent markings transferring through onto the next form
- Blank spaces should not be left on the CRF, if data are unavailable 'Unknown', 'Missing' or 'Not Done' should be recorded. Ambiguous phrases such as 'not available' should be avoided.

- All entries should be accurate, legible and verifiable with the source data (e.g. medical record)
- If legitimate differences exist between the source data and the CRF, and the CRF entry is correct, the anomaly should be explained and significance noted in the CRF
- For laboratory values outside the reference range or some other range pre-identified in the study protocol, or if a value shows significant variation from one assessment to the next, significance (if any), should be noted in the CRF along with a record of the action taken e.g. a letter was sent to the participant's GP. A copy of the letter should be kept in the participant's medical records.
- Where applicable CRFs should be signed and dated by an authorized individual to confirm capture of correct data

4.2 Corrections/Amendments

Entries should never be over-written, nor correction fluid used. Corrections should be made as per the following procedure:

1. The incorrect entry should be crossed through with a single line so the original text is still legible.
2. Correct data should then be recorded.
3. Initials and date of change should be supplied beside the update.
4. An explanation of the correction should be provided if it is not obvious why the change was made

As a general rule, amendments to data recorded on CRFs should always be handled at Site. Exceptionally the **Chief Investigator** or the **Trial Manager** could amend a CRF if this is agreed in writing AND a copy of the changed CRF is then sent to the local Site.

An exception would be updates made to data supplied on the CRF as a result of a site query issued during CRF review and/or data cleaning. All queries confirming a change to data captured on the original CRF must be signed and dated by an authorized individual at Site. If required, amendments could be made to the data on the CRF, with date of change, initials of person making the change and reference made to the Data Verification Site (DVS) Report number.

5 ASSOCIATED FORMS AND TEMPLATES

Form ID	Title of Form

6 REVISION HISTORY

SOP Number	Effective date	Revision summary
DM 09_01	**05-Dec-2011**	Existing SOP2/005 Case Report Form (CRF): Design, Completion and Correction was split into two SOPs – Case Report Form (CRF): Design, Development and Deployment SOP DM 02 & Case Report Form (CRF): Completion and Correction SOP DM 09. Moderate rewording of the Procedure from that captured on the original SOP.

7 APPENDICES

Not Applicable.

8 ARCHIVING INFORMATION

Decommissioning/Archiving Information	
Replaced by:	Signature of SOP Administrator:
Date replaced:	Date:

Drug Handling: Delivery, Storage, Distribution and Destruction

1) Receipt

The study medication will arrive at the Primary Care Clinical Trials Unit (PC-CTU) by courier from Mawdsleys. Upon arrival the contents of the delivery will be checked to ensure the product has arrived in satisfactory condition and the Record of Receipt of Study Medication form (version 1.0, 24th Feb 2011) will be completed.

2) Storage

Study medication will be stored at the PC-CTU in a secure, restricted access location.

3) Randomisation

Each bottle of study medication will be labelled with a Medication ID number. These will be printed by Mawdsleys from a list of already randomised Medication IDs in a password protected file sent to them by an independent statistician. The trial team will be sent a list of the Medication IDs and Block Numbers. The custodians of the Randomisation List will be appointed by Dr Andrew Farmer (AF) [PC-CTU Director]. Eight bottles of medication will be allocated to each recruiting site initially and restocked as needed. PC-CTU will organise the allocation of all medication.

4) Drug allocation and delivery to Recruiting sites

PC-CTU will record drug allocation using Sortition. If possible, a screen print of the "pack list" showing the allocated drugs will be printed and checked prior to any study medication leaving the PC-CTU, otherwise a Drug Allocation Log will be completed. The allocated study medication will be delivered to recruiting sites by trial staff or individuals nominated by the trial team (e.g. courier, research network staff). On receipt, one or two members (see point 5) of staff at the recruiting site will check the mediation ID numbers of the bottles they have been given and sign to acknowledge receipt. It may be necessary to redistribute trial medication from one recruiting site to another; however this should be avoided if possible. See point 9 regarding drug redistribution.

5) Drug accountability and distribution to participants

An allocation report can be printed using Sortition. This report can be printed, signed, dated and filed as a record of accountability. If a printer is not available a Site Drug Accountability Log will have been provided to recruiting sites. The recruiting site will have been instructed on how to correctly complete drug accountability documentation when randomising each participant. Drug accountability documentation will record the following information for each participant: Date of allocation, ARCHIE ID, Medication ID, dosage (x ml twice daily for 5 days), and signature of health care professional who allocated medication. If possible a second member of site staff will check the ARCHIE ID and Medication ID numbers for each medication bottle dispensed and countersign the drug accountability documentation.

6) **Drugs no longer required for the trial**

All trial medication no longer required for the study, and trial medication which has passed its expiry date, must be stored separately from unused trial medication available to be dispensed during the trial, until destruction can be arranged.

7) **Drug destruction**

Sites should follow their internal procedures for the destruction of returned and/or expired trial medication. The drug destruction log should be completed with the following details: Date, Medication ID, expiry date, and staff initials to confirm destruction.

8) **Drug Return Log**

In the event that medication needs to be returned to the PC-CTU a drug return log must be completed to document the Medication ID and must include a minimum of one release signature (recruiting site staff), and one receipt signature (PC-CTU staff). The drug destruction will then be carried out according to Working Instruction 06 (formerly called TSP 06 Destruction of Returned or Unused Drugs).

9) **Drug Redistribution**

In the event that medication needs to be redistributed from one recruiting site (origin recruiting site) to another (new recruiting site), a drug redistribution log must be completed to document the Medication ID and must include a minimum of one release signature (origin recruiting site staff), one transporter signature and one receiving signature (new recruiting site staff).

	NAME	TITLE	SIGNATURE	DATE
Written by:	Tricia Carver	Senior Clinical Trial Manager		22 Sept 2014
Reviewed by:	Faye Alexander	Clinical Trial Manager		22/SEP/2014
Approved by:	Maria Breen	Head of Trials		24 Sept 14

Destruction of Returned or Unused Drugs to coordinating centre from sites

1) Drug Return to PC CTU from sites

Where on-site destruction is not possible the site should discuss returning the medication with the University of Oxford Primary Care Clinical Trials Unit (PC-CTU) trial manager or CI. The return of the medication will be arranged by trial staff using individuals nominated by the trial team (e.g. courier, research network staff).

A drug return log must be completed to document the Medication ID and must include a minimum of one release signature (Site staff), and one receipt signature (PC-CTU staff).

2) Storage

On return to PC-CTU the trial medication will be stored in a locked cupboard in a secure restricted access location until allocation to the CI or delegate for destruction.

3) Drug Destruction

The drug to be destroyed will be accounted for on a Trial Unit Drug Destruction Log recording the Medication ID and a minimum of one release signature (PC-CTU staff). The personnel responsible for drug disposal at the designated site will document the destruction by signing off in block (one signature for the log, not per bottle of medication) and obtain one witness sign off, also in block.

	NAME	TITLE	SIGNATURE	DATE
Written by:	Tricia Carver	Senior Clinical Trial Manager		27 Sept 2014
Reviewed by:	Faye Alexander	Clinical Trial Manager		22 SEP 2014
Approved by:	Maria Breen	Head of Trials		24 Sept 14

Emergency unblinding procedure for individual participants - Site version

1) A hard copy of the individual randomisation codes (one envelope per bottle of IMP) will be supplied in sealed envelopes by Mawdsleys when they supply the blinded medication. The envelopes will be stored in a fireproof locked box located in a restricted access, locked room within the Primary Care Clinical Trials Unit (PC-CTU).

2) Access will be restricted to the trial statistician who will act as custodian for the randomisation sequence. This role will be delegated in his absence. The custodian will hold keys to the locked box in a separate, secure location.

3) The responsible clinician will report all SAEs to the PC-CTU within 24hrs of becoming aware of the event by completing an SAE report. The PC-CTU will acknowledge receipt. If the reporting site doesn't receive a receipt within 1 working day of reporting the SAE, they should telephone the trial office, 01865 617 842.

4) The Chief Investigator (CI), Dr Kay Wang (KW) or a designated representative known to the Oxford trial office, will be responsible for investigating and evaluating all adverse events reported to the PC-CTU and assessing the need for unblinding.

   i. Seriousness, causality and expectedness should be evaluated as though the patient was on active drug. Cases that are considered serious, unexpected and possibly, probably or definitely related (i.e. possible SUSARs) would require unblinding.

   ii. Unblinding should also occur where a serious adverse event has occurred and the treatment allocation is required in order to enable clinical treatments to be planned.

   iii. Unblinding should also occur in the event of other unforeseen emergencies.

5) If unblinding is deemed necessary the CI or designated representative will inform the trial co-ordinator and the custodian of the randomisation code.

6) The custodian of the randomisation code will notify the relevant responsible clinician of the treatment allocation for the relevant participant. The custodian will **not** inform the trial investigators or trial co-ordinator of whether the participant was in the Co-amoxiclav 400/57 or placebo arm of the trial.

7) The code will be accessible during office hours (9am to 5pm) Monday to Friday, excluding public holidays.

8) If the code is inadvertently un-blinded during the conduct of the trial, this will be fully documented in the trial master file.

9) All unblinding of the code for specific patients and for specific reasons will also be fully documented in the patient notes (using the Participant Unblinding Form) and in the trial master file.

	NAME	TITLE	SIGNATURE	DATE
Written by:	Tricia Carver	Senior Trial Manager		24 Sept 14
Approved by:	Maria Breen	Head of Trials		24 Sept 14.
Approved by:	Ly-Mee Yu	Lead Trial Statistician		24/9/2014

ARCHIE Nose and Throat Sampling Working Instruction

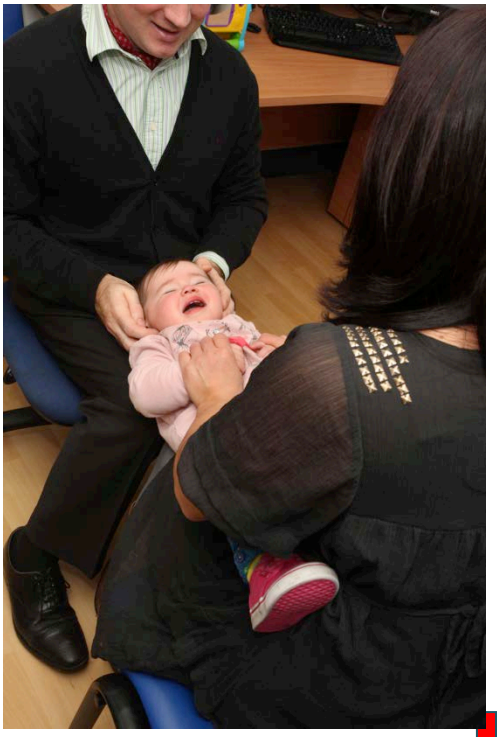
Introduction

- Proper prior preparation prevents poor performance.
- Check swab kits are in date.
- Set up environment, lay out equipment prior to bringing parent and child into room so as to minimise contact time and so reduce stress for you, the parent and the child.
- First sampling after recruitment (T1) involves taking **both a nose swab and a throat swab**.
- **All subsequent samples are throat swabs only** taken at 3 months (T2), 6 months (T3) and 12 months (T4) after start of treatment.
- **Consent** The parent/guardian must have signed the appropriate ARCHIE consent form prior to T1 sampling. For follow-up throat swabs the parent/guardian must also have checked point 8 on the study consent form. Where verbal consent is given at telephone follow-up, an additional consent form must be completed stating agreement to follow-up swabs.
- The subject/parent/guardian reserves the absolute right to withdraw from ARCHIE at any time during the study period. To avoid loss to follow up, such subjects should be offered the option to withdraw from further throat swabs while continuing to contribute to other parts of the study.
- Personal protective equipment (PPE) must be used in line with Public Health England (PHE) recommendations.
- **Take the nose swab first. The nose swab has priority in the protocol.**
- Document any deviations from protocol and adverse events on the appropriate record sheets.
- **Please review the training video for further information.**

PE and infection control requirements

Check current HPE guidelines. At the time of writing, it is recommended that irrespective of vaccination history, the operator should wear:

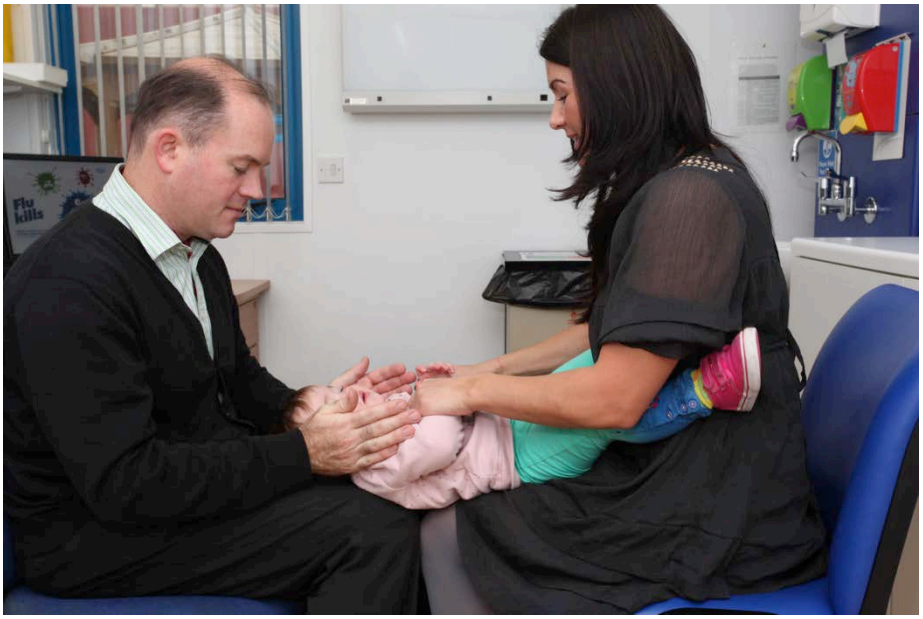
- Disposable gloves
- Standard fluid-repellent face mask
- In addition eye protection and a gown should be worn when there is a risk of splashes onto the face. This risk increases with younger children <5yrs and is particularly high with toddlers and infants <2 years.



Positioning the child

1. For infants and those under two years old:
    a. The parent/guardian should sit with knees together.
    b. The infant/young child should sit facing the parent/guardian with their legs around and over the adults thighs and have a cuddle. This reassures the child and minimises stress to Mum and research staff.
    c. The researcher should sit level and knee-to-knee with the parent/guardian.

d. When ready the infant can then be lowered to lie flat with arms held by the parent/guardian and head stabilised by the researcher.

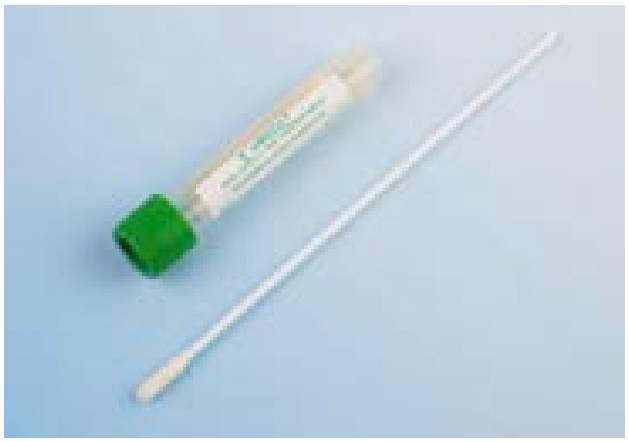


2. For young children age over two years old: The child should sit on the adult's lap, facing forward. The adult should place one arm around the child's chest & arms and the other arm's hand over the forehead to stabilise the head.

3. For older children: sit the child upright in a chair placed against a wall. Tilt their head back slightly, resting the head against a wall.

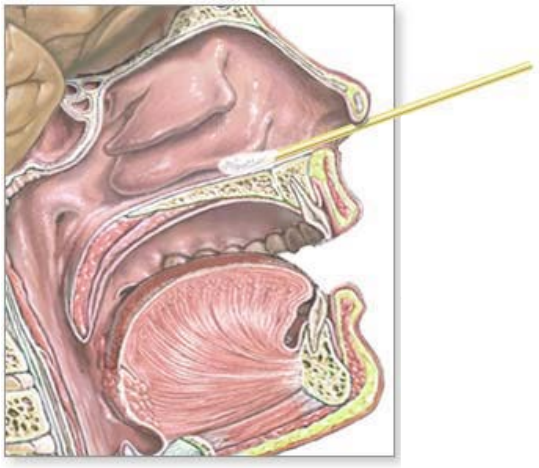
Please review the training video for further information.

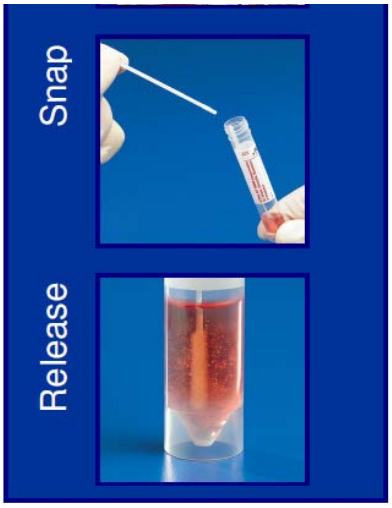
Nose & Throat Swab Sample collection, packing and dispatch



Nose swab The nose swab pack is green

1. **Equipment**:
   a. **Σ-**Virocult®, a small sterile cellular foam swab and green topped tube containing 1.0ml of viral transport medium.
   b. A box of disposable tissues.
2. Inform the family that you are going to perform a nose swab by inserting the tip of a small swab 2cm into the nose.
3. Explain that although uncomfortable, the procedure should not be painful. The most common side effects are nasal irritation and watering eyes. Both are very short lived.
4. Some people report that shutting their eyes during the procedure lessons discomfort, so say "Children find it helps to shut their eyes when we do the nose swab. You can shut your eyes if you like".
5. We don't want loads of mucous (snot). We want cells from the inside of the nose. There is often profuse nasal discharge so wipe the nose or ask the child to blow their nose prior to the inserting the swab.
6. Open up the green nose swab pack. Take care not to touch the swab tip against anything.
7. Insert the swab horizontally 1.5 to 2 cm into one nostril, rotate against the anterior medial nasal septal and turbinate mucosa for 3 seconds, repeat this procedure using the same swab in the other nostril, withdraw and place the swab in the viral transport media tube.
4. Snap the swab stick against the side of the tube.
5. Replace the green screw top on the tube. Finger tighten to prevent leaks in transport.
6. Discard the swab handle and tissue in a clinical waste bin.
7. Proceed without undue delay to take the throat swab.

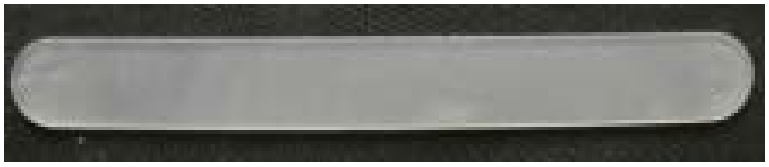




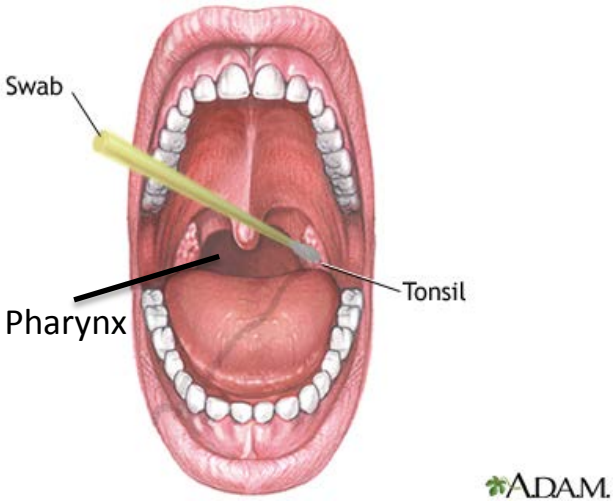
Nose & Throat Swab Sample collection, packing and dispatch

Throat swab The throat swab kit is purple

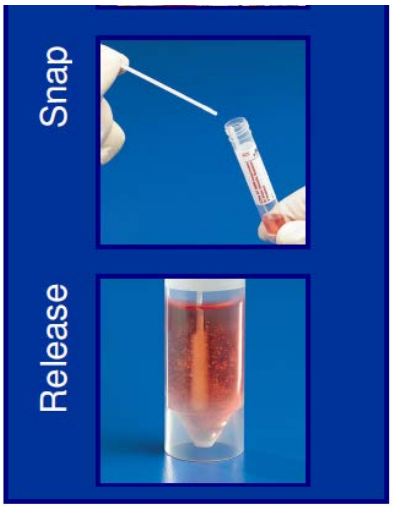
1. **Equipment:**
   a) **Σ-**Transwab®, a small sterile cellular foam swab and purple topped tube containing 1.0ml bacterial transport medium.
   b) Tongue depressor.
   c) A pen torch or good light source above and behind researcher, but not directly shining at subject.
2. Inform the family that you are going to perform a throat swab by wiping the back and sides of the throat with a small swab.



3. Explain that although uncomfortable, the procedure should not be painful. The most common side effect is a reflex gag or baulk. Both are very short lived.
4. Open up the purple throat swab kit. Take care not to touch the swab tip against anything.
5. Firmly press down the anterior half of the tongue with a tongue depressor. Do not rub or press on the posterior tongue as this will stimulate a gag reflex and can stimulate a vomit!
6. Older children can be asked to say “Ahh” to elevate the uvula and ease access to the posterior pharyngeal wall.
7. Avoiding the soft palate and tongue, wipe the sides of both tonsils and then sweep the posterior pharyngeal wall with the swab.

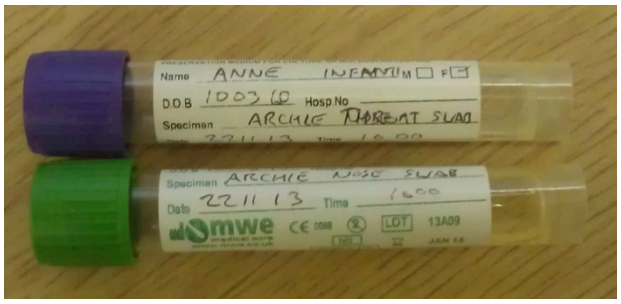


8. Take care not to poke the back of the throat, as this will cause severe pain. A child exhibiting pain is likely to result in withdrawal of the child from the study.
9. Avoiding the soft palate and tongue, withdraw the swab and place in the bacterial transport media.
10. Snap the swab stick against the side of the tube.
11. Replace the purple screw top on the tube. Finger tighten to prevent leaks in transport.
12. Discard the swab handle, tongue depressor in the clinical waste bin.
13. Next remove gloves, then mask and place in the clinical waste bin
14. Dispose of any packaging in a general waste bin.



Please review the training video for further information.

Nose & Throat Swab Sample collection, packing and dispatch



Sample handling

1. Check screw tops are secure.
2. Complete clinical details in full on both sample tubes i.e. Name, Date of Birth, Specimen = ARCHIE THROAT or ARCHIE NOSE, Date and time of specimen.
3. Attach an ARCHIE research label to each tube.
4. Complete the ARCHIE Specimen request form in full.
   Ensure GP details are completed.
5. **Research Staff must PRINT, Sign and date the specimen bag with their own details**:
   i.e. A GOODNURSE , *A Goodnurse*, 2.11.13.
6. Put both specimen tubes in the specimen bag and seal by pulling off the red strip and closing over the flap.
7. Put the bag and the specimen request form in the transport box and close.
8. Seal the box with security tab.
9. Put the sealed box in on street Royal Mail Post Box
10. The typical English ambient temperature in Winter varies between +2°C and +8°C with and average of +5°C, so for our study an outside Royal Mail post-box makes a very practical place to store samples prior to transport. The transport media contains preservative.
11. When the last post on a Saturday is missed or there is a holiday or an outside postbox is not available, the sample box should be refrigerated at +4°C and every effort made to catch first post on the next working day.

The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care

Alder Hey Children's NHS Microbiology Department	Microbiology Department Alder Hey Children's NHS Foundation Trust Eaton Road West Derby Liverpool L12 2AP 0151 228 4811	DX 6961702 Old Swan 90L www.alderhey.nhs.uk	ARCHIE

Senders Information

GP name, Address & Contact Number
Dr AS Dr Ash
The Stanley Road Medical Centre
Botley
OX7 9PQ

ARCHIE ID
L9879

Patient / Information — Please use BLOCK CAPITALS

NHS Number.....*321 654 345 346*..... Surname.....*INFANTI*..... Forename.....*ANNE*.....

Date of Birth.....10.03.10..... Address:.....*4 STANLEY ROAD BOTLEY*.....

Male ☐ Female ☒ ..... *OX7 8UY* .....

Sample information

	Study entry	3 months	6 months	12 months
Date Sample Taken	*22.11.13*			
THROAT Swab (Bacterial Culture) Purple	✔			
High NASAL Swab (Viral PCR) GREEN	✔	NA	NA	NA

21Oct v0.4

Nose & Throat Swab Sample collection, packing and dispatch

	NAME	TITLE	SIGNATURE	DATE
Written by:	Calum Semple	Lead Microbiology WG		25.09.2014
Reviewed by:	Janet Clark	Respiratory Research Nurse Alder Hey Children's NHS Foundation Trust		25.09.2014
Approved by:	CHRISTINE GERRARD	MICROBIOLOGY LABORATORY MANAGER - ALDER HEY	C Gerrard	26-9-14

Randomisation Process

- Participants will be randomised to receive either Co-amoxiclav 400/57 or Placebo by their recruiter using 'Sortition', the University of Oxford Primary Care Clinical Trials Unit (PC-CTU) in-house web-based randomisation system.

- Staff required to use Sortition will be given training instructions by web based audio-visual presentation or during a site initiation.

- Sortition will send an email notification to the Trial Manager at the PC-CTU each time a participant has been randomised.

- Emergency randomisation is not available if Sortition is offline. If you experience any difficulties with using Sortition, please report these immediately to the Trial Manager (Tel: 01865 617842).

- Access to Sortition can be gained in the following ways:
    1. The recruiter accesses Sortition him or herself via www.archiestudy.com
    2. The recruiter asks another healthcare professional to access Sortition and inform the recruiter of the medication ID allocated.
    3. The recruiter asks a member of trial staff at PC-CTU to access Sortition (Tel 01865 617842) and inform the recruiter of the medication ID allocated.

  Options 2 or 3 may be used if the recruiter is recruiting a child at a venue other than the recruiting site (e.g. the child's home). Otherwise, option 1 is the preferred option for accessing Sortition.

- If the recruiter accesses Sortition via option 2 or 3, they should also:
    a) Ensure that the healthcare professional or member of PC-CTU staff who will be accessing Sortition for them is aware of and will be contactable by telephone at the time they are due to meet with the child and his or her parent/guardian to obtain written consent and perform the eligibility and baseline assessments.
    b) Take a recruitment pack to the venue at which they will be meeting with the child and his or her parent/guardian. The recruiter may fill in paper copies of the eligibility assessment form and baseline assessment form at the recruitment venue,

but should enter these data onto the online forms as soon as possible and file the paper copies in their Investigator Site File

c) Take the **entire supply** of trial medication from the recruiting site to the venue at which they will be meeting with the child and his or her parent/guardian. This ensures that the recruiter will have the medication bottle with the medication ID generated by Sortition with them to allocate to the child. It is the recruiter's responsibility to ensure that study medication is transported correctly and securely.

d) Complete all drug accountability documentation as usual following WI 01 (formerly called TSP 01).

	NAME	TITLE	SIGNATURE	DATE
Written by:	Tricia Carver	Trial Manager		22 Sept 2014
Reviewed by:	David Judge	Clinical Trials Programmer	David Judge	23 Sept 2014.
Approved by:	Maria Breen	Head of Trials		24 Sept 14.

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

Serious Adverse Event Reporting

The procedure for reporting serious adverse events is documented in the study protocol. This working instruction is designed to be used by the trial team at each research site.

1) Download a **Serious Adverse Event (SAE) Report Form** from www.archiestudy.com or make a copy of the master form provided in the investigator site file.

2) Complete the **SAE Report Form** and submit it to PC CTU by fax (01856 617 939) or email (archie@phc.ox.ac.uk) within 24 hours of becoming aware of the event.

3) For each SAE, please also record the event on the Adverse Event Report Log and complete an online Adverse Event Report Form.

4) The PC CTU will contact you for further information. Please contact Tricia Carver (ARCHIE trial manager) on 01865 617842 if you have not been contacted within one working day of submitting the SAE Report Form.

5) The PC CTU will direct your SAE Report Form to the Chief Investigator (Dr Kay Wang) or designated representative, who will complete an evaluation and assessment of the event.

6) The PC CTU will notify the Site of the outcome of this assessment.

7) The Site will supply any additional information as requested from the MHRA, Research Ethics Committee, Sponsor or PC CTU.

	NAME	TITLE	SIGNATURE	DATE
Written by:	Tricia Carver	Trial Manager		22 Sept 2014
Reviewed by:	CLARE RIDDLE	QA MANAGER		22/SEPT/2014
Approved by:	Maria Breen	Head of Trials		24 Sept 14.

Eligibility assessment and recruitment tips

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

www.archiestudy.com

Dr Kay Wang
ARCHIE Study Chief Investigator
E-mail: kay.wang@phc.ox.ac.uk

Patients to consider for ARCHIE

- 'At risk' children aged 6 months to 12 years
- Cough AND fever* during influenza season (October to March)
- Within 5 days of symptom onset
- No known contraindication to co-amoxiclav
- Does not require immediate antibiotics or hospitalisation

*Reported as symptom or temperature 37.9°C or higher during consultation

Full eligibility criteria

FOR HEALTHCARE PROFESSIONALS

INCLUSION CRITERIA
EXCLUSION CRITERIA
DATABASE SEARCH INSTRUCTIONS
FIND GP SURGERY
SAFETY REPORTING INSTRUCTIONS

RANDOMISE YOUR PATIENT

ELIGIBILITY FORM
WEB RANDOMISATION
FOLLOW-UP DATA COLLECTION
HIGH NASAL AND THROAT SWAB TECHNIQUES
TRAINING
USEFUL DOCUMENTS

Full eligibility criteria

FOR HEALTHCARE PROFESSIONALS

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DATABASE SEARCH INSTRUCTIONS
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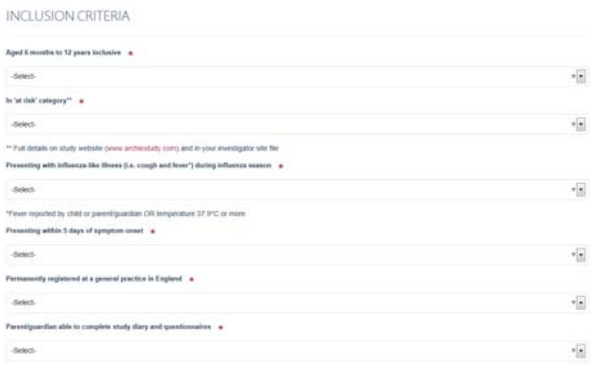
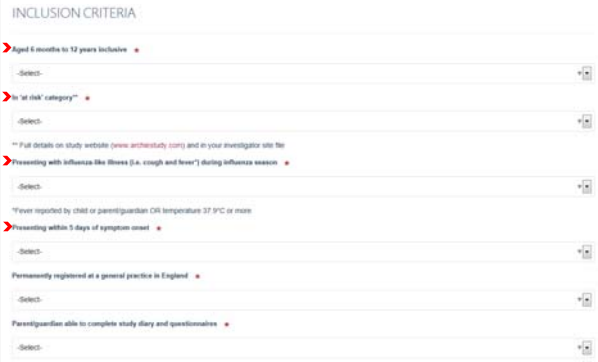
ELIGIBILITY FORM
WEB RANDOMISATION
FOLLOW-UP DATA COLLECTION
HIGH NASAL AND THROAT SWAB TECHNIQUES
TRAINING
USEFUL DOCUMENTS

Inclusion criteria



Inclusion criteria

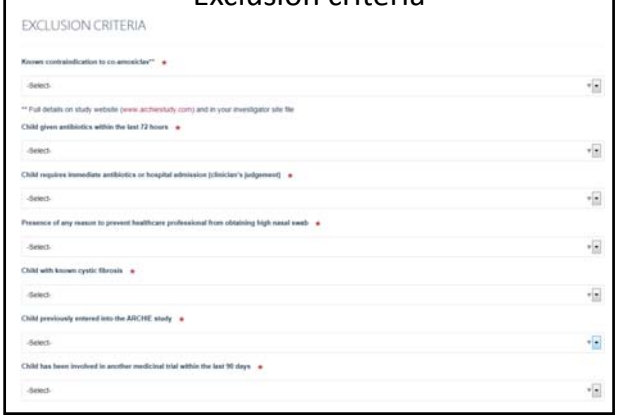


Key 'at risk' categories

(see INCLUSION CRITERIA link)

- **Prematurity in children aged 6 to 23 months** – born at less than 37 weeks' gestation
- **Immunodeficiency** – drugs, haematological conditions, malignancy, sickle cell disease
- **Diabetes mellitus**
- **Neurological conditions** – compromising respiratory function/handling of respiratory secretions
- **Lung conditions** – asthma requiring controller therapy, recurrent viral wheeze, hospitalisation within last 12 months (asthma, bronchiolitis). **NOT cystic fibrosis.**
- **Cardiac conditions** – being actively managed or monitored by specialist hospital team

Exclusion criteria



Contraindications to co-amoxiclav

See EXCLUSION CRITERIA link

- Known hypersensitivity to beta-lactam antibiotics or clavulanic acid
- History of jaundice or hepatic impairment due to co-amoxiclav
- Severe liver disease with jaundice, increased bleeding risk, bilirubin >50 micromol/litre (2 measurements within last 12 months)
- Known or suspected infectious mononucleosis
- Known phenylketonuria
- Any medication interactions
- eGFR less than 30 ml/min/1.73m^2

Recruitment timeframe

- Same day if possible
- Following (working) day if still eligibility criteria
  - Complete eligibility assessment form on the same day as the baseline assessment.

Telephone consultation
- Initial eligibility assessment
- Introduce study (information leaflets on www.archiestudy.com)

Study website

Screen prompts (EMIS Web)

Face to face consultation
- Full eligibility assessment
- Baseline assessment

Consider booking longer appointment or appointment at end of surgery

Screen prompt (EMIS Web)

- Consulting with any of the following:
  - Cough
  - Pyrexia
  - Influenza
  - Influenza-like illness
  - Upper respiratory tract infection
  - Viral illness
- Provided:
  - Age 6 months to 12 years
  - Coded 'At risk of influenza-related complications' (EMISNQAT42)

Record interest 'in principle'

The early use of Antibiotics in 'at Risk' CHildren with InfluEnza

ARCHIE

www.archiestudy.com

I might be interested in letting my child join the ARCHIE Study if they get flu

Child's Name:_____

Child's date of birth:_____

Please leave your completed slip at reception so we can record your interest.

Interest card 9Aug13 v1 REC13/NW/0621

Baseline assessment

Consent and clinical details

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

www.archiestudy.com

Dr Kay Wang
ARCHIE Study Chief Investigator
E-mail: kay.wang@phc.ox.ac.uk

Consent

- Consent from parent/guardian (compulsory)
  - Initial beside each point if agree
- +/- assent from child (optional)
- Study information leaflets available from www.archiestudy.com
  - Ask parents and children to read leaflets before baseline appointment if possible

Special points

8. Optional: I agree to allow my child to have throat swabs taken three months, six months and twelve months after entering this study and for non-cellular material from these swabs to be stored and used by the research team for further research and analysis. ☐

TOP COPY for recruiting site*, MIDDLE COPY for parent/guardian, BOTTOM COPY for University of Oxford
****GP surgeries:* keep hard copy in site file and scanned copy in child's electronic medical record.**
****GP out-of-hours centres/Trust departments:* keep hard copy in site file and fax copy to child's GP surgery.**

GP surgery notification letter

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

This study is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference RP-PG-1210-12012)

Dear Dr _____,

RE:
Name of patient:
Patient's date of birth:

This patient was entered into the ARCHIE trial on (insert date): _____ at

(insert location or stamp):_____

GP walk-in centre/Hospital department (delete as appropriate).

The ARCHIE trial is a double-blind randomised placebo-controlled trial to determine whether giving a five-day course of co-amoxiclav to 'at risk' children at an early stage during an influenza-like illness reduces the likelihood of them needing to re-consult due to clinical deterioration. For further details, please see the study website:
www.archiestudy.com

Please record the following details in your patient's medical notes:

Site ID: _____
ARCHIE ID: _____
Medication ID: _____

Please find enclosed a copy of your patient's consent form. Please retain this in your patient's medical record.

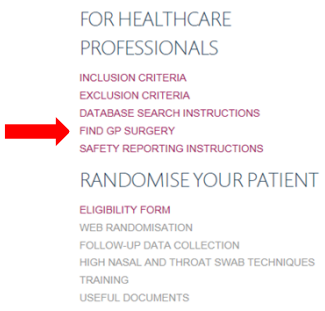
Please note that your patient's parent/guardian has given consent for us to gather information from your patient's medical notes. A member of the ARCHIE research team will contact you to arrange a suitable time and way of doing this.

Please get in touch with us if you have any questions.

Many thanks,
The ARCHIE team

Instructions for healthcare professional recruiting patient:
Please fax this letter to the patient's GP and to the ARCHIE team (01865 617 935).
Please keep the original letter in your site file.

Finding GP surgery contact details

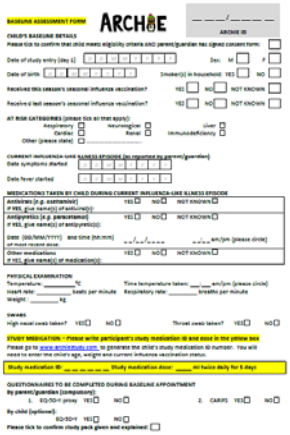


FOR HEALTHCARE PROFESSIONALS

INCLUSION CRITERIA
EXCLUSION CRITERIA
DATABASE SEARCH INSTRUCTIONS
FIND GP SURGERY
SAFETY REPORTING INSTRUCTIONS

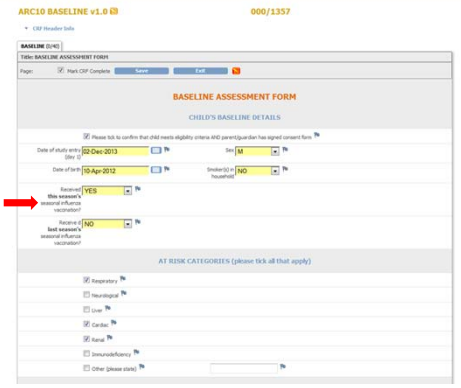
RANDOMISE YOUR PATIENT

ELIGIBILITY FORM
WEB RANDOMISATION
FOLLOW-UP DATA COLLECTION
HIGH NASAL AND THROAT SWAB TECHNIQUES
TRAINING
USEFUL DOCUMENTS



Accessing online baseline assessment form

Patient details

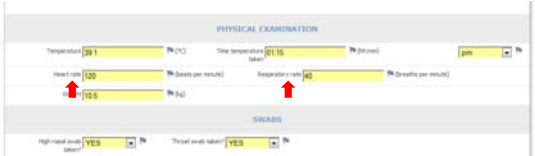


Current influenza episode

Temperature

- Use any thermometer appropriate for child's age
  - Axillary thermometer provided in each study pack
- Record time using 12 hour clock
- Select am/pm

Heart rate and respiratory rate



- Count for one minute

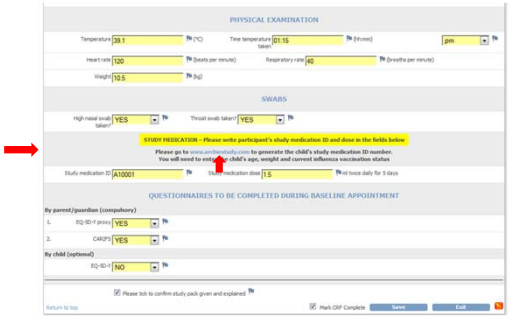
Weight

- In babies:
  - (Adult's weight + baby's weight) – Adult's weight
  - Use latest weight recorded in red book

Swabs

- Must obtain high nasal swab in order to randomise child
- Swabs will be analysed in Liverpool

Study medication



Thank you for listening

Baseline assessment

Study medication
Contact card

ARCHIE

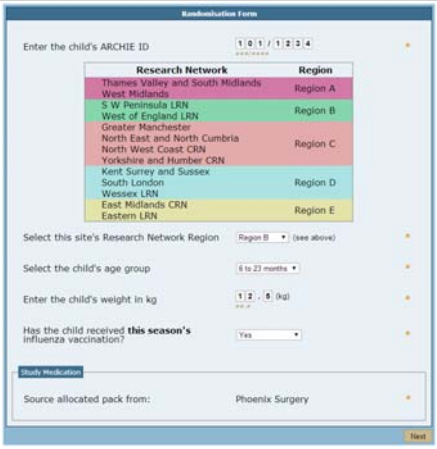
The early use of Antibiotics in at Risk CHildren with InfluEnza

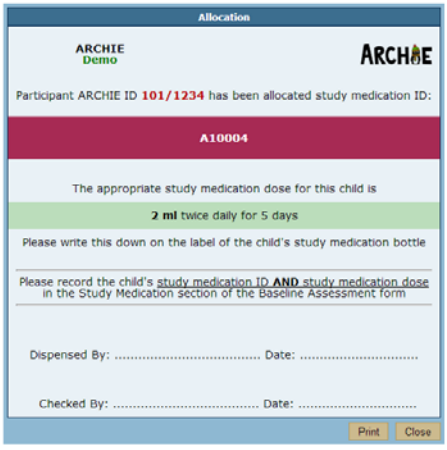
www.archiestudy.com

Dr Kay Wang
ARCHIE Study Chief Investigator
E-mail: kay.wang@phc.ox.ac.uk

Study medication dosing regimen

Age	Dosing regimen
6 months to 23 months • 6.0 to 7.9 kg • 8.0 to 10.9 kg • 11.0 to 12.9 kg	 1 ml twice daily for 5 days 1.5 ml twice daily for 5 days 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





ARCHIE Demo

ARCHIE

Participant ARCHIE ID **111/2222** has been allocated study medication ID:

A10016

Please select the appropriate study medication dose from the following table and write this down on the label of the child's study medication bottle

Child's age	Study medication dose
2 to 6 years	**2.5 ml** twice daily for 5 days
7 to 12 years	**5 ml** twice daily for 5 days

Please record the child's study medication ID **AND** study medication dose in the Study Medication section of the Baseline Assessment form

Dispensed By: ..... Date: .....

Checked By: ..... Date: .....

ARCHIE Demo

ARCHIE

Participant ARCHIE ID **111/2222** has been allocated study medication ID:

A10016

Please select the appropriate study medication dose from the following table and write this down on the label of the child's study medication bottle

Child's age	Study medication dose
2 to 6 years	**2.5 ml** twice daily for 5 days
~~7 to 12 years~~	~~**5 ml** twice daily for 5 days~~

Please record the child's study medication ID **AND** study medication dose in the Study Medication section of the Baseline Assessment form

Dispensed By: ..... Date: .....

Checked By: ..... Date: .....

Drug accountability log

Primary Care Clinical Trials Unit

ARCHIE

DRUG ACCOUNTABILITY LOG

Trial title:	The early use of Antibiotics in at Risk CHildren with InfluEnza	EudraCT number:	2013-002822-21
Trial Chief Investigator	Dr Kay Wang	Dose form and strength	Twice daily for 5 days 6 months to 23 months • 6.0 – 7.9 kg 1 ml • 8.0 – 10.9 kg 1.5 ml • 11.0 – 12.9 kg 2 ml 2 to 6 years 2.5 ml 7 to 12 years 5 ml
IMP name:	Co-amoxiclav or placebo		
Expiry Date:			
Dispensing site:		Local Principal Investigator:	

Date	Archie ID	Medication ID	Dose	Dispensed by	Checked by

ID number stickers

ARCHIE ID:
Med ID:
Dose:_____mls
Week 1 Diary

ARCHIE ID:
Med ID:
Dose:_____mls
Medication Bottle

Dispensing study medication

- Need 61 ml water for contents of one bottle
  - Measuring cup and syringe provided
- Add half of water first and shake bottle
- Add remaining water and shake bottle again
- Affix medication bottle sticker

Instructions for parent/guardian

- Give first dose asap
- Explain dosing regimen
- Discard any leftover medication after 10 doses given
- If child vomits within 30 minutes of dose can give another dose

Contact card

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

Insert child's name is taking part in the ARCHIE study (www.archiestudy.com) and was given study medication (co-amoxiclav or placebo) to take for 5 days starting on ___/___/____.

Archie ID: _____ /_____

Medication ID: _____ cc 14May14 v2.1

Contact card

Information for clinicians: If you think this child has had an adverse reaction to his/her study medication:

- Please **STOP** the study medication.
- Please prescribe a **non beta-lactam antibiotic** if antibiotics are clinically indicated.
- Please see our website for instructions on reporting **suspected adverse reactions to study medication.**

Local investigator: *Insert phone number of GP surgery or hospital*

Contact telephone number: 01865 617 842 (trial office)

Thank you for listening

Baseline assessment

Questionnaires and diaries
Arranging follow-ups

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

www.archiestudy.com

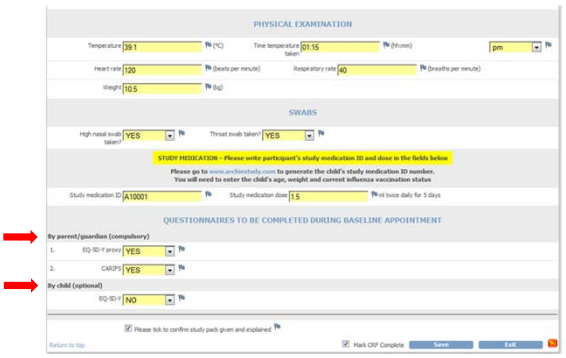
Dr Kay Wang
ARCHIE Study Chief Investigator
E-mail: kay.wang@phc.ox.ac.uk

While you prepare study medication….

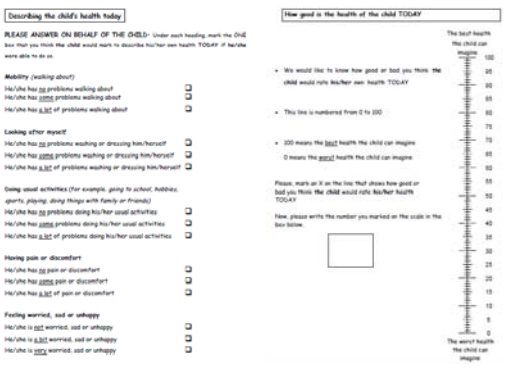
Let parents and children look at our Study Diary – Instructions and Overview

Ask parents and children to fill in their questionnaires and contact information form

Questionnaires

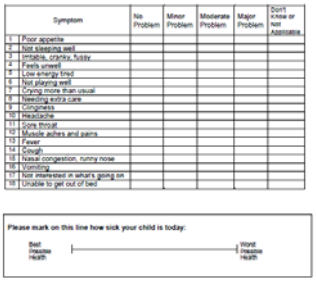


EQ-5D-Y proxy (parent/guardian)

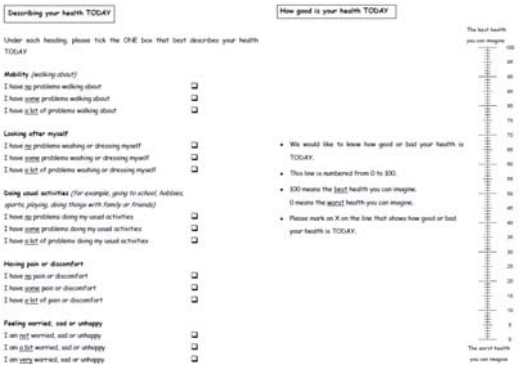


CARIFS (parent/guardian)

Canadian Acute Respiratory Infections and Flu Scale



EQ-5D-Y (child, optional)



Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility *(walking about)*
- I have no problems walking about
- I have some problems walking about
- I have a lot of problems walking about

Looking after myself
- I have no problems washing or dressing myself
- I have some problems washing or dressing myself
- I have a lot of problems washing or dressing myself

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*
- I have no problems doing my usual activities
- I have some problems doing my usual activities
- I have a lot of problems doing my usual activities

Having pain or discomfort
- I have no pain or discomfort
- I have some pain or discomfort
- I have a lot of pain or discomfort

Feeling worried, sad or unhappy
- I am not worried, sad or unhappy
- I am a bit worried, sad or unhappy
- I am very worried, sad or unhappy

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.

The best health you can imagine

The worst health you can imagine

Contact information

- Participant details
  - Name
  - NHS number
- Contact details for participant's GP
  - Name
  - Address
  - Telephone number

Study diaries

- Weeks 1, 2, 3, 4 (for parent/guardian to complete)
- Postal return is preferred option
  - Pre-paid envelopes x4
- Study diary for child (optional)

Study diary (parents/guardians)

Study Diary - Week 1

Archie ID: _____

To be completed by healthcare professional:

Day of study entry (day 1): Day of week_____Date (dd/mm/yyyy)_____

Key days to remember for filling in this diary:

Day 4 Day of week_____Date (dd/mm/yyyy)_____

Day 7 Day of week_____Date (dd/mm/yyyy)_____

Medication dose: _____

Medication timings (approximate):

Morning dose to be given at (hh:mm): _____

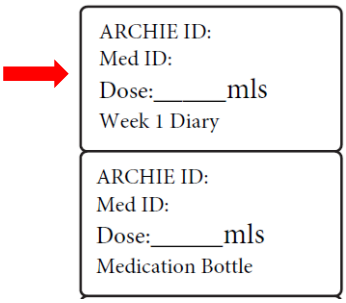
Evening dose to be given at (hh:mm): _____

IMPORTANT INFORMATION

Please DO NOT give your child more than 10 doses of study medication.

Please discard any unused study medication after you have given your child 10 doses.

ID number stickers



ARCHIE ID:
Med ID:
Dose:_____mls
Week 1 Diary

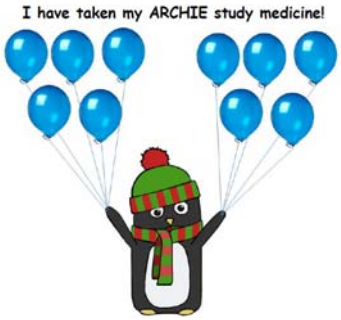
ARCHIE ID:
Med ID:
Dose:_____mls
Medication Bottle

Contents of diary

- Duration of illness
  - Symptoms
  - Temperature
  - Study medication
  - Other medication
- Weekly questions
  - Potential side-effects
  - Daily activities and childcare
  - Health service contacts
- Questionnaires
  - EQ-5D-Y proxy: days 4, 7, 14 and 28
  - CARIFS: day 7

Electronic axillary thermometer

Study diary for child (optional)



Study diary for child (optional)

Follow-ups (all participants)

- Week 1 (telephone)
  - Day 7 to 10
- Week 2 (telephone)
  - Day 14 to 17
- Day 1 = date of randomisation
- (Mobile phone text reminders – days 4, 7, 14, 21, 28)

Follow-up throat swabs (optional)

- 3, 6 and 12 months (+/- 2 weeks)
- Study team will remind GP surgery when swabs are due and send swab kits

Thank you for listening

Follow-up assessments
Adverse Event Reporting

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

www.archiestudy.com

Dr Kay Wang
ARCHIE Study Chief Investigator
E-mail: kay.wang@phc.ox.ac.uk

Follow-up assessments

- Telephone follow-ups
  - Week 1 (day 7 to 10)
  - Week 2 (day 14 to 17)
- Objectives
  - Safety monitoring
  - Reminders to complete and return diaries
  - (Consent for additional throat swabs)

Before you pick up the phone….

8. Optional: I agree to allow my child to have throat swabs taken three months, six months and twelve months after entering this study and for non-cellular material from these swabs to be stored and used by the research team for further research and analysis. ☐

….check if parent gave consent for additional throat swabs

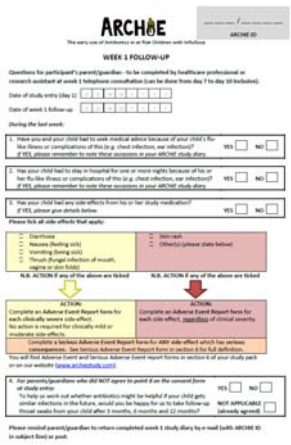
Follow-up forms

FOR HEALTHCARE PROFESSIONALS

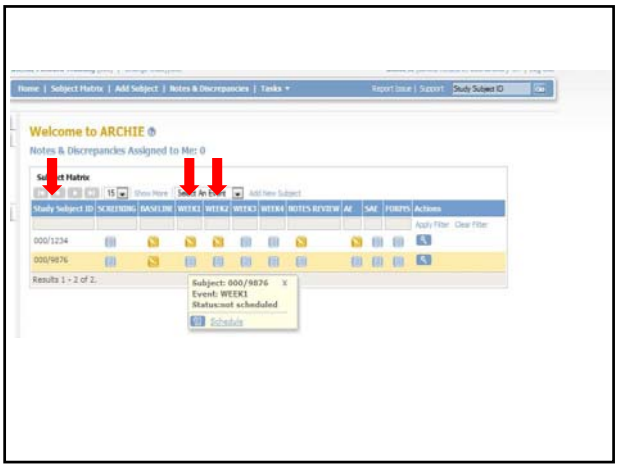
INCLUSION CRITERIA
EXCLUSION CRITERIA
DATABASE SEARCH INSTRUCTIONS
FIND GP SURGERY
SAFETY REPORTING INSTRUCTIONS

RANDOMISE YOUR PATIENT

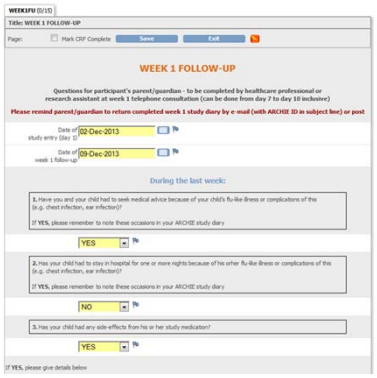
ELIGIBILITY FORM
WEB RANDOMISATION
FOLLOW-UP DATA COLLECTION
HIGH NASAL AND THROAT SWAB TECHNIQUES
TRAINING
USEFUL DOCUMENTS


ARCHIE

WEEK 1 FOLLOW-UP



Follow-up (Q1-3)



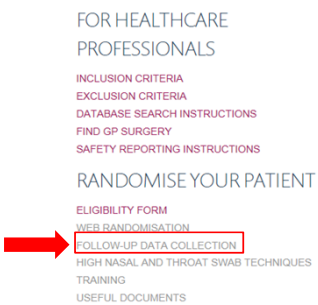
Which side-effects do I report?

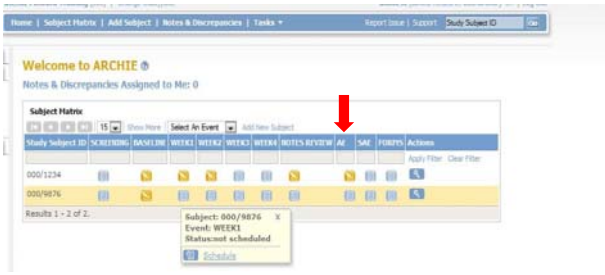
- Common known side-effects
  - Diarrhoea, nausea, vomiting and thrush
  - Only report if:
    - Clinically severe (based on clinician's judgement)
    - Result in a serious adverse event
- Other side-effects
  - Always report

Adverse event reporting

- Record each adverse event on participant's **Adverse Event Report Log (study pack)**
- Complete and submit an **Adverse Event Report Form (online)**

Follow-up forms





Serious adverse event reporting

FOR HEALTHCARE PROFESSIONALS

INCLUSION CRITERIA
EXCLUSION CRITERIA
DATABASE SEARCH INSTRUCTIONS
FIND GP SURGERY
SAFETY REPORTING INSTRUCTIONS

RANDOMISE YOUR PATIENT

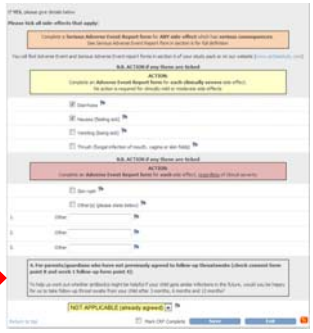
ELIGIBILITY FORM
WEB RANDOMISATION
FOLLOW-UP DATA COLLECTION
HIGH NASAL AND THROAT SWAB TECHNIQUES
TRAINING
USEFUL DOCUMENTS

Report serious adverse events within 24 hours of becoming aware of the event

Study diary reminders

- Week 1
  - Check parent/guardian has completed:
    - Day 4 and day 7 questionnaires
    - Weekly questions
- Week 2
  - Check parent/guardian has completed:
    - Day 14 questionnaire, weekly questions
  - Remind parent/guardian to complete:
    - Week 3 and week 4 diaries (including day 28 questionnaire)

Additional throat swabs (Q4)



Obtain written consent at 3 month appointment

Thank you for listening

Medical notes review

ARCHIE

The early use of Antibiotics in at Risk CHildren with InfluEnza

www.archiestudy.com

Dr Kay Wang
ARCHIE Study Chief Investigator
E-mail: kay.wang@phc.ox.ac.uk

Accessing online notes review

FOR HEALTHCARE PROFESSIONALS

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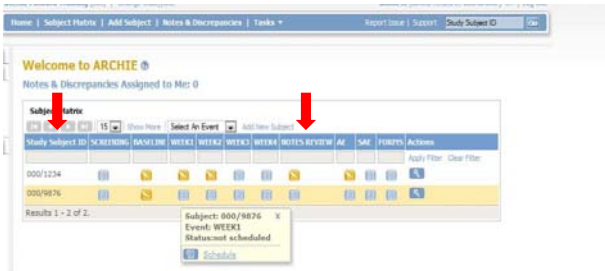
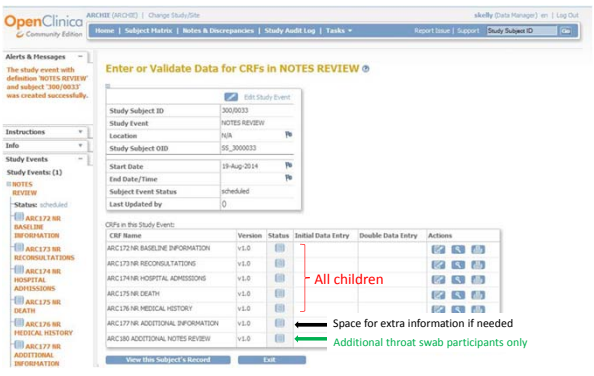
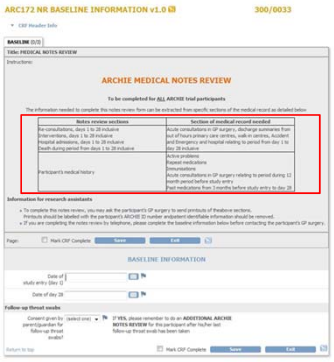




Baseline information



Re-consultations

N.B. Check scanned documents as well as consultations section of medical notes to identify re-consultations

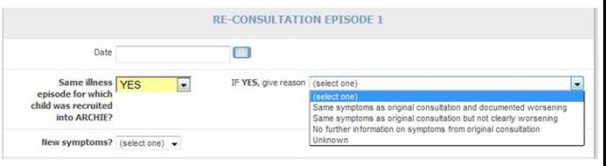
Same symptoms as original presentation but worsening

Primary outcome: Re-consultation due to clinical deterioration

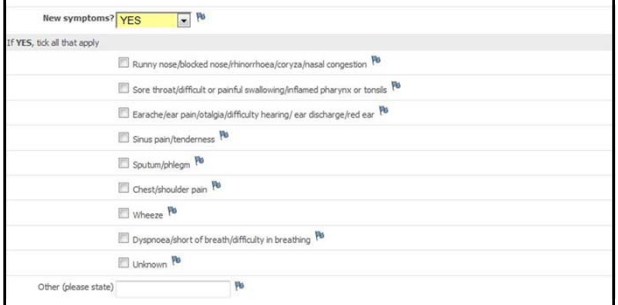
Development of complications requiring medication or hospitalisation

Development of new symptoms

Reason for re-consultation



New symptoms

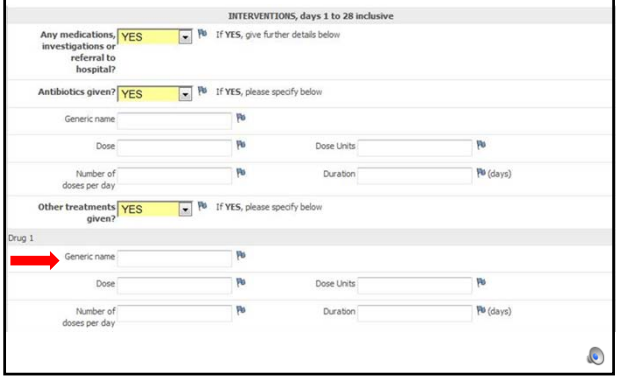


New diagnoses

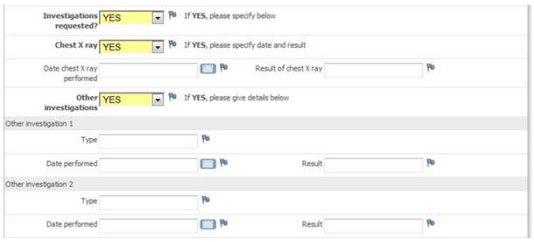
Interventions

- Medications
- Investigations
- Referrals for acute hospital admission

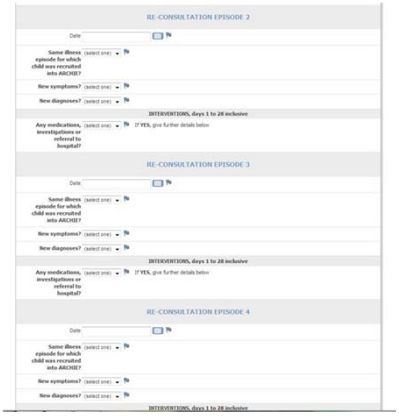
Medications



Investigations



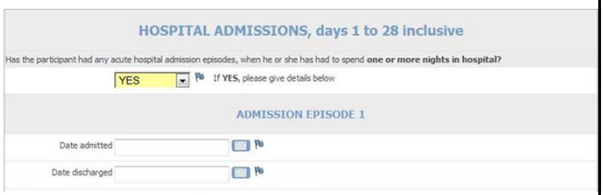
Referral for acute admission



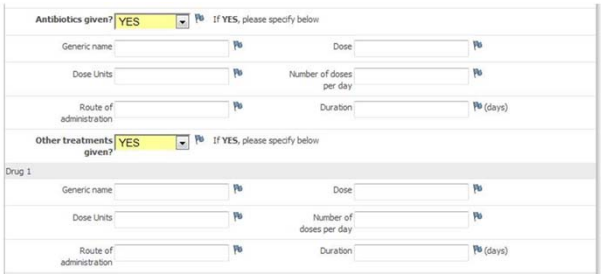
Hospital admissions and deaths

- Hospital admission = any acute admission to hospital for one or more nights from day 1 to day 28
- Remember to report serious adverse events if not already done so

Hospital admissions



Antibiotics and other treatments

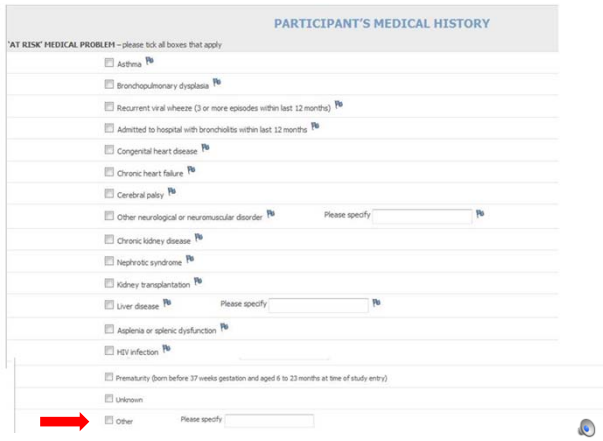


Investigations

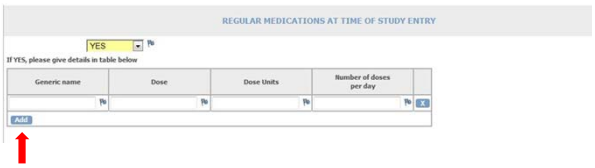
Intensive Care Unit admissions

Medical history

- 'At risk' medical problem
- Regular medications at time of study entry
- Vaccinations
- Acute consultations during 12-month period before study entry
- Antibiotics given during 3-month period before study entry



Regular medications



Vaccinations

- Haemophilus influenzae b (Hib)
- Pneumococcal conjugate vaccine (PCV)
  - Prevenar or Prevenar 13
- Influenza
  - Same season as recruited
  - Previous season
  - Pandemic

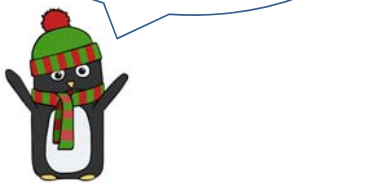
Acute consultations

Antibiotics

Additional notes review

- Only required for children from whom additional throat swabs obtained
- Antibiotics up to 12 months after study entry
  - Follow-up throat swab timings: 3, 6, 12 months

Thank you for listening



Primary Care
Clinical Trials Unit

ARCHIE

SUPPLIES INFORMATION

You will not need to re-order supplies for ARCHIE.

When your supplies drop to less than 6 study packs, you will automatically be sent 3 new packs containing the recruitment documents and study medication.

Tricia Carver

ARCHIE Trial Manager
Nuffield Department of Primary Care Health Sciences, University of Oxford

RESEARCH SERVICES
Clinical Trials and Research Governance
Joint Research Office
Block 60
Churchill Hospital
Headington
Oxford
OX3 7LE

12.08.13

Dear Sir/Madam,

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

REC Ref: 13/NW/0621

IRAS Lock Code: 121769/488269/1/157

EudraCT Number: 2013-002822-21

The above study has been designed by Dr Kay Wang and colleagues at the University of Oxford and funded by the NIHR. I confirm that the University will accept the role of Research Sponsor of this Study in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and Amendment 2006.

Insurance-provided indemnity arrangements are in place for the project ; Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered :WD1200463

Sponsorship is confirmed subject to the condition that the following are sent to Clinical Trials and Research Governance for review prior to submission to the Research Ethics Committee. Failure to do so may compromise insurance cover for the project.

- Any substantial amendment
- Any extension to the study end date
- Addition of any new research site or patient identification centre

In addition annual progress reports & annual safety reports must be copied to Clinical Trials and Research Governance.

Any communications relating to Research Sponsorship should be directed to the undersigned, whose contact details are given in this letter.

Yours faithfully

Ms H House
Head of Clinical Trials and Research Governance

General Enquiries Tel: +44 (0)1865 572221 · Direct Line Tel: +44 (0)1865 572245
Fax: +44 (0)1865 572228 · Email: Heather.house @admin.ox.ac.uk · Web: www.admin.ox.ac.uk/researchsupport/ctrg/

RESEARCH SERVICES
Joint Research Office, Block 60, Churchill Hospital, Old Road, Headington, Oxford OX3 7LE

UNIVERSITY OF OXFORD

To whom it may concern

Ref.

Date: 1st August 2014

Dear Sir/Madam

I am writing to confirm that clinical research activity Sponsored by the University of Oxford is insured through various legal liability and associated insurances, the policy schedule for which is attached. This insurance expires on 31 July 2015, and it is the University's present intention to maintain this insurance or a replacement with similar terms and conditions in place into the future.

Yours faithfully

Graham Waite
Insurance Officer

Tel: +44 (0)1865 572209
Fax: +44 (0)1865 572215 Email: graham.waite@admin.ox.ac.uk Web: www.admin.ox.ac.uk/researchsupport

SCHEDULE

Policy No :	WD1400450
The Insured :	University of Oxford
Address :	University Offices Wellington Square Oxford OX1 2JD United Kingdom
Business :	The undertaking of any **Trial** by or on behalf of the **Insured** in connection with the **Insured's** business
Broker :	Aon UK Limited 8 Devonshire Square, Cutlers Gardens, London, EC2M 4PL, United Kingdom
Period of Insurance :	a) From 01 August 2014 To 01 August 2015 b) Any subsequent period for which the **Insured** shall pay and the **Underwriters** shall agree to accept a renewal premium Both days at 12.01 Local Standard Time at principal address
Limits of Liability :	SECTION 1 No Fault Compensation Policy GBP 10,000,000 any one claim SECTION 2 Clinical Testing Legal Liability Policy GBP 10,000,000 any one claim Should a claim involve more than one Section the total liability of the Underwriters shall not exceed GBP 10,000,000 in the aggregate for any one Period of Insurance Including the applicable Extended Discovery Period plus Legal Costs. The Limits of Liability are inclusive of Deductible
First Premium :	As per Individual Security Details.
Policy Territory :	Worldwide
Deductible :	GBP 10,000 each and every claim or USD 25,000 each and every claim within the jurisdiction of United States of America and Canada
Memoranda applicable at Inception :	As shown in Risk Details
Retroactive Date :	01 August 2005

3.3 Insert Site Contract Agreement

3.4 Insert Service Support Cost information

Health Research Authority

National Research Ethics Service

NRES Committee North West - Liverpool East
HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7832
Facsimile: 0161 625 7299

10 October 2013

Dr Kay Wang
University of Oxford
Radcliffe Observatory Quarter
Woodstock Road
Oxford
OX2 6GG

Dear Dr Wang

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**

Thank you for your letter of 01 October 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Miss Helen Penistone, nrescommittee.northwest-liverpooleast@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter from Tricia Carver		12 August 2013
REC application - 121769/488269/1/157		09 August 2013
Protocol	1	09 August 2013
Investigator CV - Kay Yee Wang		09 August 2013
Participant Information Sheet: Information leaflet for parents and guardians	1	09 August 2013
Participant Information Sheet: Short PIL for parents/guardians	1	09 August 2013
Participant Information Sheet: What is the ARCHIE Study about? Video	1	
Participant Information Sheet: Information for Children	1	09 August 2013
Participant Consent Form: Consent form for parents/guardians	1	09 August 2013
Participant Consent Form: Consent form for follow-up throat swabs for parents/guardians	1	09 August 2013
Participant Consent Form: Assent Form	1	09 August 2013
GP/Consultant Information Sheets	1	09 August 2013
Sample Diary/Patient Card	Diary intro v1	09 August 2013
Sample Diary/Patient Card	Diary wk1 v1	09 August 2013
Sample Diary/Patient Card	Diary wk 2 v1	09 August 2013
Sample Diary/Patient Card	Diary wk3 v1	09 August 2013
Sample Diary/Patient Card	Diary wk4 v1	09 August 2013
Sample Diary/Patient Card	Child diary v1	09 August 2013
Other: Electronic communication	1	09 August 2013
Other: Week 1 follow-up	1	09 August 2013
Other: Week 2 follow-up	1	09 August 2013
Other: ARCHIE Certificate		
Advertisement	Pre-season short leaflet v1	09 August 2013
Advertisement	Poster	09 August 2013
Advertisement	Interest card v1	09 August 2013
Evidence of insurance or indemnity	Letter from Ms H House	12 August 2013
Response to Request for Further Information		01 October 2013
Participant Information Sheet: Information leaflet for parents and guardians	2	01 October 2013
Sample Diary/Patient Card	Patient Card v2	27 September 2013
Other: ARCHIE Baseline Assessment Form	1.1	27 September 2013
Evidence of insurance or indemnity		01 August 2013
Letter from Sponsor from Ms H House		12 August 2013

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.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

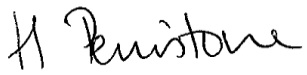
Further information is available at National Research Ethics Service website > After Review

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

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

With the Committee's best wishes for the success of this project.

Yours sincerely



On behalf of
Mrs Glenys J Hunt
Chair

Email: nrescommittee.northwest-liverpooleast@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Ms Heather House
University of Oxford

Dr Lorna Henderson
Oxford Health NHS Foundation Trust

From:	Henderson Lorna (RNU) Oxford Health
To:	Kay Wang
Cc:	Tricia Carver; CTRG Sponsorship Correspondence; tvclrn@nhs.net; tvp.crp@nhs.net
Subject:	NIHR CSP- Ref 121769 - Governance Reviews Complete
Date:	15 November 2013 15:01:48

Dear Dr Kay Wang,

Re: 121769 - The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE

We are writing to inform you that all study-wide governance criteria have been undertaken for your study. When the local governance criteria have been completed for each participating NHS organisation, each R&D office will be provided with a Governance Report which includes all the necessary information to grant NHS Permission.

Please note that you cannot commence the study at a particular site **until you have received a letter of NHS Permission for that site.**

For further information regarding how to notify us of any amendments to the study please refer to the Amendments Guidance for Researchers at http://www.crncc.nihr.ac.uk/about_us/processes/csp.

Please contact us if you require any further information.

Kind regards.
Lorna

Dr Lorna Henderson
Thames Valley Primary Care Research Partnership

5.2 Insert Local R & D document

Safeguarding public health

MHRA

Ms T Carver
UNIVERSITY OF OXFORD
DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
23-38 HYTHE BRIDGE STREET
OXFORD
OX1 2ET
UNITED KINGDOM

03/10/2013

Dear Ms T Carver

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our reference:	21584/0321/001-0001
Eudract Number:	2013-002822-21
Product:	BROWN & BURK Co-amoxiclav Oral Suspension 400 mg/57 mg/5 ml
Protocol number:	ARCHIE001

NOTICE OF ACCEPTANCE

I am writing to inform you that the Licensing Authority accepts your request for a clinical trial authorisation (CTA), received on 16/09/2013.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed.

Yours sincerely,

Clinical Trials Unit
MHRA

From: Clatworthy Vicki (RNU) Oxford Health
To: Tricia Carver
Subject: RE: ARCHIE
Date: 15 September 2014 14:39:05
Attachments: image001.png

Dear Tricia

Thank you for your email.

I can confirm that we have approved the undernoted amendments at both a global and local level (Former Thames Valley PCT's).

Amendment 1 dated 11 February 2014
Amendment 2 dated 12 March 2014 (new sites)
Amendment 3 dated 23 April 2014 (new sites)
Amendment 4 dated 16 May 2014 (new sites)
Amendment 5 dated 19 June 2014 (new sites)
Amendment 6 dated 19 June 2014

Regards
Vicki

Vicki Clatworthy
Research Facilitator
NIHR Clinical Research Network: Thames Valley and South Midlands
Delivering research to make patients, and the NHS, better

The Farmhouse, Warneford Hosptial, Roosevelt Drive, Headington, Oxford, OX3 7JX
Tel: 07717 483009 (mobile); 01865 226625 (office)

www.crn.nihr.ac.uk/thamesvalley

**** Please note new website address - please update your favourites! ****

From: Tricia Carver [mailto:tricia.carver@phc.ox.ac.uk]
Sent: 10 September 2014 10:43
To: Clatworthy Vicki (RNU) Oxford Health
Subject: ARCHIE

Hi Vicki,

I have a huge favour to ask. I am trying to put together over 100 site files in an efficient way to save printing. To assist this I wanted to ask if you could provide me with a one page letter confirming the approval of all 6 amendments at both a global and local TV level? The amendments are as follows:

Amendment 1 dated 11 February 2014
Amendment 2 dated 12 March 2014 (new sites)
Amendment 3 dated 23 April 2014 (new sites)

Amendment 4 dated 16 May 2014 (new sites)
Amendment 5 dated 18 June 2014 (new sites)
Amendment 6 dated 19 June 2014 (MHRA, label modification)

Kind regards,

Tricia Carver
Senior Trial Manager

The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care
The ARCHIE study is funded by the National Institute for Health Research's Programme Grants for Applied Research Programme
Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Direct line: 01865 617 842
FAX: 01865 617 939
Website: www.archiestudy.com
Twitter: @archiestudy

Amendment 1

From: Helen Barnby-Porritt
Sent: 17 February 2014 09:39
To: Tricia Carver
Cc: Kay Wang
Subject: ARCHIE Clinical Trial Amendment 1

RE: The early use of Antibiotics in at Risk Children with InfluEnza (ARCHIE)
EudraCT Number: 2013-002822-21
Ethics Ref: 13/NW/0621

Dear Dr. Wang,

Thank you for sending CTRG your documentation for an amendment to the above trial.

I have reviewed your revised documents and am writing to confirm that the changes you propose will not affect ongoing Sponsorship or Indemnity of this trial. Please proceed with submission of your amendment to the MHRA and REC.

Best wishes
Helen

Dr Helen Barnby-Porritt
Research Support Associate | CTRG
University of Oxford
JRO, Block 60, Churchill Hospital, Oxford, OX3 7LE
T: +44 01865 572225 F: +44 01865 572228 E: Helen.Barnby-porritt@admin.ox.ac.uk
www.admin.ox.ac.uk/researchsupport/ctrg

** Please note new working hours 7.45am to 2.15pm Mon - Fri **

Health Research Authority
National Research Ethics Service

NRES Committee North West - Liverpool East

HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7827
Fax: 0161 625 7299

07 March 2014

Ms Tricia Carver
Department of Primary Care Health Sciences
University of Oxford
23-38 Hythe Bridge Street
Oxford
OX1 2ET

Dear Ms Carver

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:	**ARCHIE_SA0001**
Amendment date:	**11 February 2014**
IRAS project ID:	**121769**

The above amendment was reviewed by the Sub-Committee in correspondence. Approval was sought for changes to the protocol:

- The definition of suitable recruitment sites has been changed from "primary care" has been changed to "primary care and other equivalent ambulatory care settings".
- Accountability of the Trial Treatment has been edited to reflect the responsibilities of Mawdsley Brooks & Co., who will import the placebo and perform the blinding and repackaging.
- The Programme Steering Committee will function as the Trial Steering Committee.
- Department name updated to include "Nuffield" prefix.

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.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter from Tricia Carver		12 February 2014
European Commission Notification of Substantial Amendment Form	ARCHIE_SA0001	11 February 2014
Protocol	2 (clean & tracked)	12 February 2014
MHRA confirmation that they do not consider the amendment to be substantial		19 February 2014
Email from sponsor confirming amendment does not affect sponsorship or Indemnity of the trial		17 February 2014

Membership of the Committee

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

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

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 NRES 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
Professor Neil Pender
Vice-Chair

Email: nrescommittee.northwest-liverpooleast@nhs.net

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

Copy to: Dr Kay Wang, University of Oxford
Dr Lorna Henderson, Oxford Health NHS Foundation Trust
Heather House, Oxford University Hospitals

NRES Committee North West - Liverpool East

Attendance at Sub-Committee of the REC meeting on 06 March 2014

Name	*Profession*	*Capacity*
Professor Neil Pender (Chair)	Professor of Orthodontics	Expert
Dr Peter Walton	Lay Member	Lay

Also in attendance:

Name	*Position (or reason for attending)*
Miss Helen Penistone	Co-ordinator

Thames Valley Primary Care Research Partnership

Hosted by Oxford Health NHS Foundation Trust
The Farmhouse
Warneford Hospital
Roosevelt Drive
Headington
Oxford
OX3 7JX

Tel: 01865 226625
Fax: 01865 226638
e-mail: tvp.crp@nhs.net

Dr Kay Wang
University of Oxford
Department of Primary Care Health Sciences
Radcliffe Observatory Quarter
Woodstock Road
Oxford OX2 6GG

18 March 2014

Dear Dr Wang,

Re: Study 13/NW/0621 – The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE – CSP 121769

I have been notified of amendment 1 dated 11 February 2014. Having reviewed the documents and ethics document dated 7 March 2014 I can confirm that the governance approval dated 16 January 2014 remains in force and now includes the amendment number stated in this letter.

Yours sincerely,

Lorna R Henderson

Dr Lorna Henderson
Research Management & Governance Manager

Amendment 2

Thames Valley Primary Care Research Partnership

Hosted by Oxford Health NHS Foundation Trust
The Farmhouse
Warneford Hospital
Roosevelt Drive
Headington
Oxford
OX3 7JX

Tel: 01865 226625
Fax: 01865 226638
e-mail: tvp.crp@nhs.net

Dr Kay Wang
University of Oxford
Department of Primary Care Health Sciences
Radcliffe Observatory Quarter
Woodstock Road
Oxford OX2 6GG

18 March 2014

Dear Dr Wang,

Re: Study 13/NW/0621 – The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE – CSP 121769

I have been notified of amendment 2 dated 12 March 2014. Having reviewed the documents and ethics document dated 14 March 2014 I can confirm that the governance approval dated 16 January 2014 remains in force and now includes the amendment number stated in this letter.

Yours sincerely,

Lorna R Henderson

Dr Lorna Henderson
Research Management & Governance Manager

Amendment 3

Health Research Authority
National Research Ethics Service

NRES Committee North West - Liverpool East
HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7827
Facsimile: 0161 625 7299

13 May 2014

Ms Tricia Carver
Department of Primary Care Health Sciences
University of Oxford
23-38 Hythe Bridge Street
Oxford
OX1 2ET

Dear Ms Carver

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:	**3**
Amendment date:	**23 April 2014**
IRAS project ID:	**121769**

Thank you for submitting the above amendment, which was received on 06 May 2014.

Research Site	Principal Investigator / Local Collaborator
Derby City PCT, Cardinal Square, 10 Nottingham Road, Derby DE1 3QT	Dr Kay Wang
Royal Cornwall Hospital, Treliske, Truro TR1 3LJ	Dr Anne Prendiville
Yeovil District Hospital NHS Foundation Trust, Higher Kingston, Yeovil, Somerset BA21 4AT	Dr Meredith Kane
Derby Hospitals NHS Foundation Trust, Utoxeter Road, Derby DE22 3DT	Dr Gisela Robinson

The amendment relates solely to the addition of new site(s) and/or investigator(s) within the National Health Service (NHS) or Health and Social Care (HSC) in Northern Ireland. The site-specific assessment for the site(s) will therefore form part of the research governance review. The Site-Specific Information (SSI) Form for the site should be included with the application for R&D approval.

On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s) and/or investigator(s), subject to management permission being given by the relevant NHS/HSC R&D office(s) prior to the study starting at the site.

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.

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

Yours sincerely

Ms Rachel Katzenellenbogen
REC Assistant

Email: nrescommittee.northwest-liverpooleast@nhs.net

Copy to: Heather House, Oxford University Hospitals
Dr Kay Wang, University of Oxford

From:	Susan Tonks
To:	Tricia Carver
Subject:	ARCHIE amendment 3
Date:	24 April 2014 07:23:17

Dear Tricia,

Thank you for the documentation for the 3rd substantial amendment to ARCHIE.

There are no changes that would affect ongoing sponsorship, however, I would suggest that you complete section G of the NoSA prior to submission to REC, rather than simply referring to the cover letter. Please email a copy of the completed form once you have made the additions.

Please feel free to use this email as proof of sponsor awareness should it be required.

Best wishes

Susan

Susan Tonks
Senior Research Support Associate | Research Services
Clinical Trials & Research Governance
University of Oxford
T: +44 01865 572223 **E:** susan.tonks@admin.ox.ac.uk
http://www.admin.ox.ac.uk/researchsupport/ctrg/

! YˆSyŘYˆSnt п

Tricia Carver

From: Helen Barnby-Porritt
Sent: 21 May 2014 13:56
To: Tricia Carver
Subject: Re: ARCHIE substantial amendment 4

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Tricia,

Thank you for sending CTRG your documentation for an amendment to the ARCHIE trial (REC reference 13/NW/0621) to add two new sites.

I have reviewed the documentation for the proposed change and am writing to confirm that this will not affect ongoing Sponsorship of this study. Please proceed with submission of your documents to the REC for review.

Best wishes
Helen

From: Tricia Carver
Sent: 16 May 2014 15:40
To: Karl Shepherd
Subject: ARCHIE substantial amendment

Dear Karl,
Please find attached a notification for substantial amendment to the REC for the ARCHIE Study. SA004 involves the addition of new NHS sites.

Kind regards,

Tricia Carver
Senior Trial Manager

The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care
The ARCHIE study is funded by the National Institute for Health Research's Programme Grants for Applied Research Programme
Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Direct line: 01865 617 842
FAX: 01865 617 939

From:	Clatworthy Vicki (RNU) Oxford Health
To:	Kay Wang
Cc:	Tricia Carver; Henderson Lorna (RNU) Oxford Health; CTRG Sponsorship Correspondence; CLRN TV (OXFORD UNIVERSITY HOSPITALS NHS TRUST)
Subject:	NIHR CSP – Ref. 121769 - Receipt of an Amendment
Date:	18 June 2014 12:02:08

Dear Kay Wang,

Re: 121769 - The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE

Amendment 3 dated 23 April 2014 – Date of Submission to REC 23/04/14
Amendment 4 dated 16 May 2014 – Date of Submission to REC 16/05/14

Thank you for submitting the above amendment. This amendment does not require review by individual NHS Trusts in England and so you may proceed to implement the amendment at NHS Trusts in England when you have any other relevant approvals in place.

If applicable, please ensure you send copies of your regulatory approval(s) (REC, MHRA and other supporting documents) to this email address or through the IRAS document submission. We will make these available to all participating sites.

Please note that as Chief Investigator/Sponsor, it remains your responsibility to ensure the PIs at each of your sites (if applicable) are informed of this amendment.

Please contact us using the details below if you require any further information.

Kind regards

Vicki

Vicki Clatworthy
Research Facilitator
NIHR Clinical Research Network: Thames Valley and South Midlands
Delivering research to make patients, and the NHS, better

The Farmhouse, Warneford Hosptial, Roosevelt Drive, Headington, Oxford, OX3 7JX
Tel: 07717 483009 (mobile); 01865 226625 (office)

www.crn.nihr.ac.uk/thamesvalley

**** Please note new website address - please update your favourites! ****

Amendment 5

From: Helen Barnby-Porritt
To: Tricia Carver; Kay Wang
Subject: Re: ARCHIE substantial amendment SA005
Date: 19 June 2014 11:58:05
Attachments: image001.png

Dear Tricia,

Thank you for sending CTRG your documentation for an amendment (number 5) to the ARCHIE trial (REC reference 13/NW/0621) to add further new sites.

I have reviewed the documentation for the proposed change and am writing to confirm that this will not affect ongoing Sponsorship of this study. Please proceed with submission of your documents to the REC for review.

Best wishes
Helen

From: Tricia Carver
Sent: 18 June 2014 12:37
To: Karl Shepherd
Subject: ARCHIE substantial amendment SA005

Dear Karl,
Please find attached a notification for substantial amendment to the REC for the ARCHIE Study. SA005 involves the addition of new NHS sites. I was told by the REC that a cover letter is not needed.
Kind regards,

Tricia Carver
Senior Trial Manager

The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care
The ARCHIE study is funded by the National Institute for Health Research's Programme Grants for Applied Research Programme
Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Direct line: 01865 617 842
FAX: 01865 617 939

Health Research Authority
National Research Ethics Service

NRES Committee North West - Liverpool East
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7827
Fax: 0161 625 7299

24 June 2014

Tricia Carver
Senior Trial Manager
ARCHIE
Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford
OX2 6GG

Dear Ms Carver

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:	**ARCHIE_SA005**
Amendment date:	**18 June 2014**
IRAS project ID:	**121769**

Thank you for submitting the above amendment, which was received on 19 June 2014.

Research site	*Principal Investigator / Local Collaborator*
University Hospital of North Tees, Department of Paediatrics, Hardwisk Road, Stockton on Tees TS22 5GE	Vijay Tandle
Former Nottingham City PCT, attn: Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG	Kay Wang
Salisbury NHS Foundation Trust, Salisbury District Hospital, Odstock Road, Salisbury SP2 8BJ	Robert Scott-Jupp
Poole Hospital NHS Foundation Trust, Poole General Hospital, Longfleet Road, Poole BH15 2JB	Mark Tighe

The amendment relates solely to the addition of new site(s) and/or investigator(s) within the National Health Service (NHS) or Health and Social Care (HSC) in Northern Ireland. The site-specific assessment for the site(s) will therefore form part of the research governance review. The Site-Specific Information (SSI) Form for the site should be included with the application for R&D approval.

On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s) and/or investigator(s), subject to management permission being given by the relevant NHS/HSC R&D office(s) prior to the study starting at the site.

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.

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

Yours sincerely

Rachel Katzenellenbogen
REC Manager

Email: nrescommittee.northwest-liverpooleast@nhs.net

Copy to: Dr Kay Wang, University of Oxford
Heather House, Oxford University Hospitals
Dr Lorna Henderson, Oxford Health NHS Foundation Trust

From:	Clatworthy Vicki (RNU) Oxford Health
To:	Kay Wang
Cc:	CTRG Sponsorship Correspondence; Tricia Carver; Henderson Lorna (RNU) Oxford Health; CLRN TV (OXFORD UNIVERSITY HOSPITALS NHS TRUST)
Subject:	NIHR CSP – Ref. 121769 - Receipt of an Amendment
Date:	24 June 2014 14:15:56

Dear Kay Wang,

Re: 121769 - The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE - Amendment 5, 19 June 2014

Date of Submission to REC 19/06/2014

Thank you for submitting the above amendment. This amendment does not require review by individual NHS Trusts in England and so you may proceed to implement the amendment at NHS Trusts in England when you have any other relevant approvals in place.

If applicable, please ensure you send copies of your regulatory approval(s) (REC, MHRA and other supporting documents) to this email address or through the IRAS document submission. We will make these available to all participating sites.

Please note that as Chief Investigator/Sponsor, it remains your responsibility to ensure the PIs at each of your sites (if applicable) are informed of this amendment.

Please contact us using the details below if you require any further information.

Kind regards

Vicki

Vicki Clatworthy
Research Facilitator
NIHR Clinical Research Network: Thames Valley and South Midlands
Delivering research to make patients, and the NHS, better

The Farmhouse, Warneford Hosptial, Roosevelt Drive, Headington, Oxford, OX3 7JX
Tel: 07717 483009 (mobile); 01865 226625 (office)

www.crn.nihr.ac.uk/thamesvalley

**** Please note new website address - please update your favourites! ****

Amendment 6

From: Helen Barnby-Porritt
To: Tricia Carver
Subject: ARCHIE trial (REC reference 13/NW/0621) - Substantial Amendment 6
Date: 19 June 2014 15:52:21

Dear Tricia,

Thank you for sending CTRG your documentation for an amendment (number 6) to the ARCHIE trial (REC reference 13/NW/0621) to change the labelling of the trial medication and update the IMP dossier.

I have reviewed the documentation for the proposed change and am writing to confirm that this will not affect ongoing Sponsorship of this study. Please proceed with submission of your documents to the MHRA for review.

Best wishes
Helen

Dr Helen Barnby-Porritt
Research Support Associate | CTRG
University of Oxford
JRO, Block 60, Churchill Hospital, Oxford, OX3 7LE
T: +44 01865 572225 **F:** +44 01865 572228 **E:** Helen.Barnby-porritt@admin.ox.ac.uk
www.admin.ox.ac.uk/researchsupport/ctrg

** Please note my working hours are 8.30am to 4.30pm Mon - Thurs **

From: LiverpoolEast NRESCommittee.NorthWest- (HEALTH RESEARCH AUTHORITY)
To: Tricia Carver
Subject: RE: approval letter 2013-00282221
Date: 08 August 2014 16:01:47
Attachments: image005.png
image006.png

Dear Tricia

Thank you for the update.

Best Wishes
Helen

Miss Helen Penistone | REC Manager
Health Research Authority
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ
E: helen.penistone@nhs.net | T: 0161 625 7832
Your centre: HRA NRES Centre Manchester | www.hra.nhs.uk

IMPORTANT – **Click here** for details of significant changes in Spring 2014 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**

From: Tricia Carver [mailto:tricia.carver@phc.ox.ac.uk]
Sent: 04 August 2014 11:42
To: LiverpoolEast NRESCommittee.NorthWest- (HEALTH RESEARCH AUTHORITY)
Cc: CLRN TV (OXFORD UNIVERSITY HOSPITALS NHS TRUST); Karl Shepherd
Subject: FW: approval letter 2013-00282221

Dear Ethics team,
This is to inform you that we have had a substantial amendment approved by the MHRA. I have copied in the lead research network and the sponsor , for their files. We did not submit this amendment to the REC as it solely related to aspects of the medication which do not relate to participants:

- the storage of the medication at recruiting sites before the trial medication is dispensed to the participant
- The number of bottles in the production batch

Please let me know if you require more information.
Kind regards,

Tricia Carver
Senior Trial Manager
ARCHIE
The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care
The ARCHIE study is funded by the National Institute for Health Research's Programme Grants for Applied Research Programme
Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Direct line: 01865 617 842
FAX: 01865 617 939

From: Clinical Trial Helpline [mailto:ctdhelpline@mhra.gsi.gov.uk]
Sent: 01 August 2014 10:26
To: Tricia Carver
Subject: approval letter 2013-00282221

Dear Tricia

Thank you for your enquiry.

Please find attached a copy of the approval letter for the EudraCT no above.

Kind Regards
CTU Helpline

Your views matter. Please tell us what you think of the service you have received from us by following the link below:
https://www.surveymonkey.com/s/ClinicalTrialHelplineFeedback

From: Tricia Carver [mailto:tricia.carver@phc.ox.ac.uk]
Sent: 01 August 2014 10:24
To: Clinical Trial Helpline
Subject: approval letter 2013-00282221
Importance: High

Dear Ms T Carver

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	21584/0321/001-0002
Eudract Number:	2013-002822-21
Product:	BROWN & BURK Co-amoxiclav Oral Suspension 400 mg/57 mg/5 ml
Protocol number:	ARCHIE001
Substantial Amendment Code Number:	Code Number: ARCHIE_SA006
Version:	
Date: 2014/06/19	

I have just spoken to someone at your office as I had not heard back with a response for the above amendment. They tell me it was approved on the 8th and a letter sent. I never received a letter. It has been resent, but to speed things up it would be extremely helpful to have an electronic copy so we can have our labels printed.

Kind regards,

Tricia Carver
Senior Trial Manager

The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care
The ARCHIE study is funded by the National Institute for Health Research's Programme Grants for Applied Research Programme
Nuffield Department of Primary Care Health Sciences
Clinical Trials Unit
Radcliffe Observatory Quarter
Woodstock Road
Oxford, OX2 6GG

Direct line: 01865 617 842
FAX: 01865 617 939

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

mhra.gov.uk

Ms T Carver
UNIVERSITY OF OXFORD
DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
23-38 HYTHE BRIDGE STREET
OXFORD
OX1 2ET
UNITED KINGDOM

08/07/2014

Dear Ms T Carver

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	21584/0321/001-0002
Eudract Number:	2013-002822-21
Product:	BROWN & BURK Co-amoxiclav Oral Suspension 400 mg/57 mg/5 ml
Protocol number:	ARCHIE001
Substantial Amendment Code Number:	Code Number: ARCHIE_SA006
Version:	
Date: 2014/06/19	

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 02/07/2014.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

Clinical Trials Unit
MHRA

From:	Clatworthy Vicki (RNU) Oxford Health
To:	Kay Wang
Cc:	Tricia Carver; CTRG Sponsorship Correspondence; CLRN TV (OXFORD UNIVERSITY HOSPITALS NHS TRUST)
Subject:	NIHR CSP – Ref. 121769 - Receipt of an Amendment
Date:	12 August 2014 14:30:05

Dear Kay Wang,

Re: 121769 - The early use of Antibiotics in at Risk Children with InfluEnza-ARCHIE - Amendment 6, 19 June 2014

Date of Submission to MHRA 19/06/2014

Thank you for submitting the above amendment. This amendment does not require review by individual NHS Trusts in England and so you may proceed to implement the amendment at NHS Trusts in England when you have any other relevant approvals in place.

If applicable, please ensure you send copies of your regulatory approval(s) (REC, MHRA and other supporting documents) to this email address or through the IRAS document submission. We will make these available to all participating sites.

Please note that as Chief Investigator/Sponsor, it remains your responsibility to ensure the PIs at each of your sites (if applicable) are informed of this amendment.

Please contact us using the details below if you require any further information.

Kind regards

Vicki

Vicki Clatworthy
Research Facilitator
NIHR Clinical Research Network: Thames Valley and South Midlands
Delivering research to make patients, and the NHS, better

The Farmhouse, Warneford Hosptial, Roosevelt Drive, Headington, Oxford, OX3 7JX
Tel: 07717 483009 (mobile); 01865 226625 (office)

www.crn.nihr.ac.uk/thamesvalley

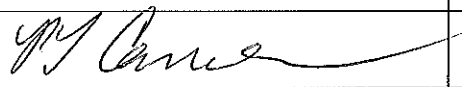
**** Please note new website address - please update your favourites! ****

Primary Care
Clinical Trials Unit

FILE NOTE

FILE NOTE TITLE:	Not present: Subject ID forms	File note ID/No.	01
Study acronym or short title:	ARCHIE		
Investigator (Site Name):	Kay Wang (University of Oxford)		
Date:	20 October 2014		

No subject ID forms exist for ARCHIE participants, because all contact details data will be entered directly into the electronic database. Section 8.1 of the ARCHIE Site File will therefore remain empty.

	Name (Job title)	Signature	Date
Signed (Author of file note)	Tricia Carver Senior Trial Manager		20 Oct 2014
Reviewed by (if applicable)	NA	NA	
Approved by	NA	NA	

Insert local document

8.2 Patient Recruitment - Informed Consent

For archiving only – all identifiable information must be kept in accordance with PC-CTU SOPs

Insert local document

8.3 Patient Recruitment - Completed CRFs (if used)

For archiving only – all identifiable information must be kept in accordance with PC-CTU SOPs

Insert local document

8.4 Patient Recruitment - Eligibility forms (if used)

For archiving only – all identifiable information must be kept in accordance with PC-CTU SOPs

Primary Care
Clinical Trials Unit

FILE NOTE

FILE NOTE TITLE:	Not present: Screening records	File note ID/No.	02
Study acronym or short title:	ARCHIE		
Investigator (Site Name):	Kay Wang (University of Oxford)		
Date:	20 October 2014		

No paper copies of patient screening records will exist for ARCHIE; this is done entirely electronically. Section 8.4 of the ARCHIE Site File will therefore remain empty.

	Name (Job title)	Signature	Date
Signed (Author of file note)	Tricia Carver Senior Trial Manager		20 Oct 2014
Reviewed by (if applicable)	NA	NA	
Approved by	NA	NA	

Primary Care Clinical Trials Unit

ARCHIE

DELEGATION LOG AND SIGNATURE FORM

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

Sponsor: University of Oxford

Ethics Number: 13/NW/0621

EudraCT Number: 2013-002822-21

Trial Chief Investigator name: Dr Kay Wang

Site / GP surgery/ Pharmacy:

By signing the form, the Chief Investigator authorises the personnel mentioned on the form to perform the assigned tasks.

Individual							PI Authorisation		Documents provided	
Name	Signature	Initials	Designation	Responsibility Codes	Start date	Stop date	PI signature	Date	CV	GCP
			PI	A,B,G,H,I,L,N,O,P,Q						

The above personnel are authorised to perform the following:

A = Subject selection/screening
B = Obtain informed consent
C = Assist in informed consent
D = Perform vital signs
E = Perform physical examinations
F = Perform measurements
G = Collect trial data
H = Clinical Record Forms entries/corrections
I = Data queries
J = Sign Clinical Record Forms (CRFs)
K = Prescribe medication/treatment
L = Dispense trial medication
M = Administer trial medication
N = Collection/handling/dispatching of specimen
O = Posting CRFs to co-ord centre
P = Maintain ISF
S = Site personnel training & support

and have responsibility to adhere to:

Q = the study protocol
R = the payment as described in the information given

Insert local document

9.1 Signed and dated delegation log

Insert local document

9.2 Signed and dated CVs

Insert local document

9.3 Evidence of GCP training

Insert local document

9.4 Evidence of study specific training (training records)

Site Training Record

Site:

Training Provided: remotely by presentations accessed on the internet

Training Components:

1 =Background, objectives and end points
2 = Investigator Site File – purpose, contents and requirements to maintain
3 =Medication storage
4 = Use of website for eligibility checking
5 = Consent/assent
6 = Taking nasal swab
7 = Taking throat swab
8 =Use of Open Clinica for CRF completion
9 = Use of Sortition to randomise participant
10= Medication dispending
11 = Diary completion
12 = Child temperature monitoring
13 = Unblinding
14 = AE reporting
15 = SAE reporting
16 = Withdrawal/discontinuation
17 = Loss to follow up

Please sign below to confirm that you have received training as detailed above; you have had the opportunity to ask questions, understand the process and feel qualified to work to the process as outlined.

Trainee Name	Training component completed	Signature	Date
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17		

Internet based training presentation can be accessed using the following urls:

Video 1 – eligibility assessment and recruitment tips

http://youtu.be/QXtPF_cAryA

Video 2 – baseline assessment consent and clinical details

http://youtu.be/kcBnJfTQ4gA

Video 3 – baseline assessment study medication and contact card

http://youtu.be/t83wbNV1zkU

Video 4 – questionnaires, diaries and arranging follow ups

http://youtu.be/Q1PPU3KWOF8

Video 5 – follow up assessment and adverse event reporting

http://youtu.be/AEE3l3jU29c

Contact Details for Access to Online Systems

Site:

Name	Email	User name (will be assigned by University of Oxford)	Please indicate access requirements		
			Study Website (Staff area) ✓	**Randomising** (sortation) ✓	**CRF Data Entry** (open clinica) ✓

The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care

ARCHIE

Simplified IMP Dossier

Quality data

Version: 2 (dated 18 June 2014)

Sponsor:
University of Oxford, Joint Research Office, Block 60, Churchill Hospital, Headington, Oxford, OX3 7LE, UK

TABLE OF CONTENTS

Introduction

In ARCHIE, the IMPs are as follow:

IMP	Marketing authorisation holder
70ml Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension	Brown & Burk UK Limited
Placebo to 70ml Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension	N/A

2.2.1.P Investigational Medicinal Product Under Test

According to Article 9(8) of Directive 2001/20/CE of 4 April 2001 and the revised detailed guidance 2010/C 82/01, this section of the IMPD is presented as *simplified IMPD* since part of the supporting documentation has been assessed previously as part of a marketing authorisation in the European Union or in an ICH country.

The MHRA granted Brown & Burk UK Limited marketing authorisation for the medicinal product 70ml Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (PL 25298/0006) on 16th August 2012.

For this trial, 70ml Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension is manufactured and packaged according to its marketing authorisation. The IMPD quality data for 70ml Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension is therefore constituted by the SmPC for 70ml Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension.

Manufacturer: Micro Labs Limited
16 Veerasandra Industrial Area
Anekal Taluk
Bangalore
Karnataka
IN-560 100
India

No modification is being made to the authorised product other than re-labelling of the product label on the bottle and repackaging of bottle into an unbranded secondary carton (See section on Packaging and Labelling).

Appendix 1 - Grant of marketing authorisation
Appendix 2 - SmPC
Appendix 3 - Certificate of GMP complicate of manufacturer – Micro Labs Ltd

6.2.1.P Placebo product

6.2.1.P.1 Description and Composition (Placebo)

Placebo to Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension.

6.2.1.P.2 Pharmaceutical Development (Placebo)

Placebo to Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (70ml) contains the same excipients as the test product. In order to match the test product for fill weight, bulk density, and viscosity, tests were carried out with different excipients ratios in order to identify the most comparable formulation.

6.2.1.P.3 Manufacture

6.2.1.P.3.1 Manufacturer(s) (Placebo)

The placebo is manufactured by the same manufacturer of the test product.

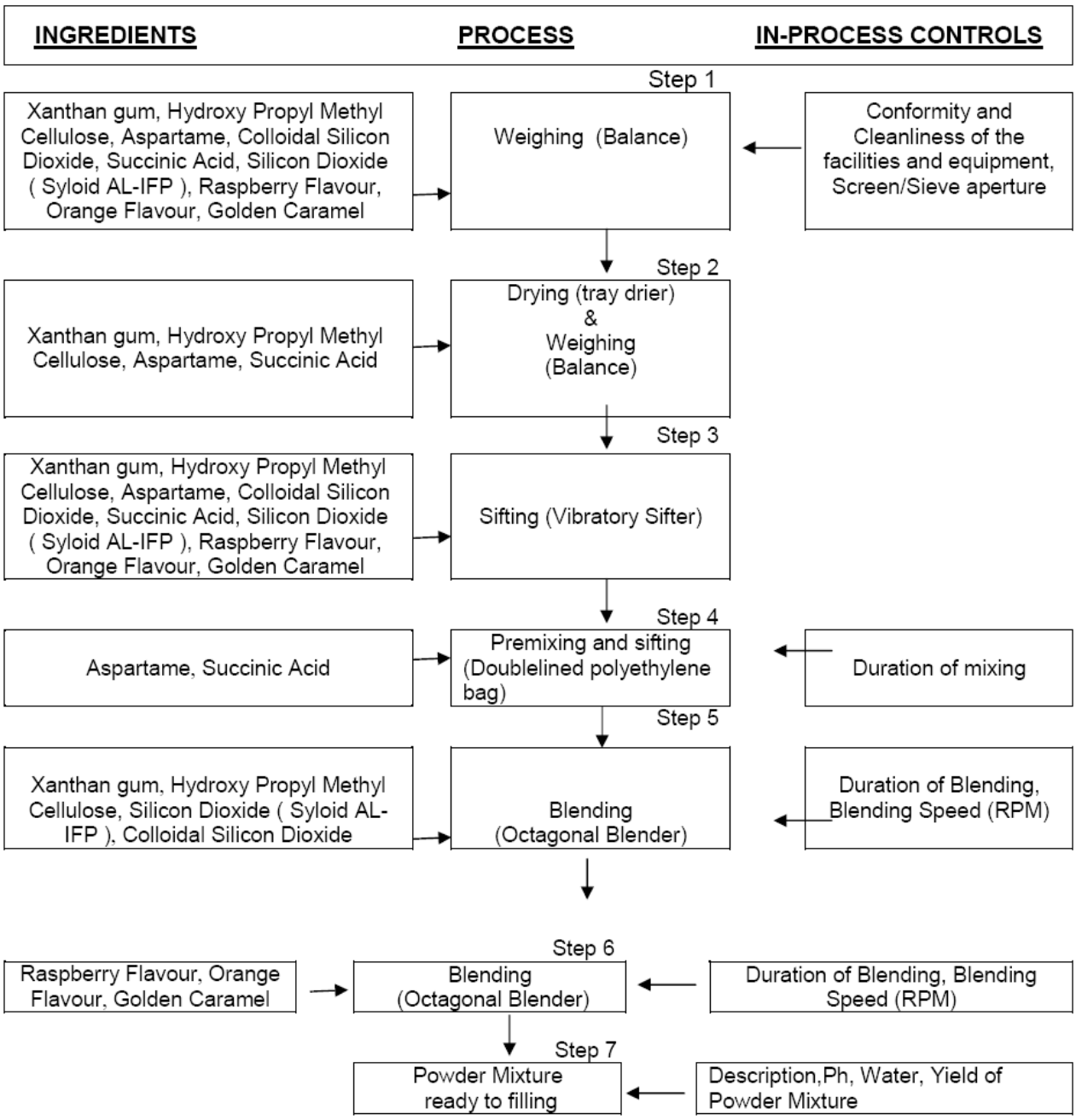
Manufacturer: Micro Labs Limited
16 Veerasandra Industrial Area
Anekal Taluk
Bangalore
Karnataka
IN-560 100
India

Mawdsley-Brooks & Company Limited (MIA(IMP) 741) is responsible for the importation and QP declaration of the placebo comparator.

6.2.1.P.3.2 Batch Formula (Placebo)

Sr. N0.	Ingredients	Grade	Item code	Rationale	Input qty per bottle in g	Overages %	Quantity for the batch (kg)
Dry mixing							
1	Silicon Dioxide (Syloid AL-IFP)	USP/NF	REND 051	Diluent	7.000	NA	45.500
2	Aspartame	Ph. Eur	REND 235	Sweetener	0.500	NA	3.250
3	Succinic Acid	USP/NF	REND 315	PH Adjuster	0.04	NA	0.260
4	Xanthan gum (Ziboxan PM 200)	Ph. Eur	REND 148	Thickener	0.05	NA	0.325
5	Hydroxy Propyl Methyl Cellulose (Methocel E5 LV)	Ph. Eur	REND 234	Thickener	1.200	NA	7.800
6	Colloidal Silicon Dioxide (Cab-o-sil M-5)	Ph. Eur	REND 141	Glidant	1.000	NA	6.500
7	Raspberry Flavour (Raspberry DC 107)	IH	REND 057	Flavour	1.310	NA	8.515
8	Orange Flavour (Orange DC 100 BB)	IH	REND 058	Flavour	1.400	NA	9.100
9	Golden Caramel (Golden Caramel 501118 AP0551)	IH	REND 059	Flavour	1.500	NA	9.750
Total Fill weight					14.00		91.000

6.2.1.P.3.3 Description of Manufacturing Process and Process Controls (Placebo)



6.2.1.P.3.4 Control of Critical Steps and Intermediates (Placebo)

In Process specification:

TEST NO.	TEST	SPECIFICATIONS
1.	Description (In house)	White to off-white powder.
2.	Water content (By KF) (Ph. Eur. method 2.5.12)	Not more than 10 %
3.	pH of the suspension (Ph. Eur. method 2.2.3)	Between 4.3 and 5.3

6.2.1.P.3.5 Process Validation and/or Evaluation (Placebo)

Not applicable

6.2.1.P.4 Control of Excipients (Placebo)

6.2.1.P.4.1 Specifications (Placebo)

Not applicable as all excipients are the same as the test product.

6.2.1.P.4.2 Analytical Procedures (Placebo)

Not applicable as all excipients are the same as the test product.

6.2.1.P.4.3 Validation of Analytical Procedures (Placebo)

Not applicable as all excipients are the same as the test product.

6.2.1.P.4.4 Justification of Specifications (Placebo)

Not applicable as all excipients are of the same as the test product.

6.2.1.P.4.5 Excipients of Animal or Human Origin (Placebo)

Not applicable as all excipients are the same as the test product.

6.2.1.P.4.6 Novel Excipients (Placebo)

There are no novel excipients used in the manufacture of the placebo comparators.

6.2.1.P.5 Control of the Placebo Product (Placebo)

6.2.1.P.5.1 Specifications (Placebo)

SPECIFICATIONS FOR STAGE – I : (INITIAL ANALYSIS)

TEST NO.	TEST	SPECIFICATIONS	
1.	Description (In house) i) Dry powder ii) Reconstituted Suspension	White to off-white powder. White to off-white suspension with fruity aromatic odour.	
2.	Mean mass (In house)	For 70ml pack	14.0 gm ± 5% (Between 13.300 g and 14.700g)
3.	Uniformity of weight (mass) of delivered doses from multidose containers (Ph. Eur. method 2.9.27)	Not more than two of the individual mass deviate from the average mass by more than 10.0 % and none deviates by more than twice the percentage (i.e. 20.0%).	
4.	pH of the suspension (Ph. Eur. method 2.2.3)	Should be between 4.0 and 6.0	
5.	Water content (By KF) (Ph. Eur. method 2.5.12)	Not more than 10 %	
6.	Microbiological quality * (Ph. Eur. method 5.1.4) A) Total Bacterial Count B) Total Fungal Count C) Pathogenic organisms Escherichia coli	 Not more than 1000 CFU / g Not more than 100 CFU / g Should be absent / g	
7.	Reconstitution time (In house)	Not more than 5 minutes.	

* Microbial limit test is monitored only for submission batches and process validation batches, thereafter every 10th batch or first batch of each year.

SPECIFICATIONS FOR STAGE II : RECONSTITUTED SUSPENSION AFTER 7 DAYS*

TEST NO.	TEST	SPECIFICATIONS
1.	Description (In house) Reconstituted suspension:	White to off-white suspension with fruity aromatic odour.
2.	pH of the suspension (Ph. Eur. method 2.2.3)	Should be between 4.0 and 6.0

6.2.1.P.5.2 Analytical Procedures (Placebo)

METHOD OF ANALYSIS

- **Instruction for reconstitution of suspension:**
  Add accurately measured specified quantity of Milli-Q water to each of the bottle. Ensure the constituted solution level is upto the mark available on bottle. Close the cap securely. Shake the bottle vigorously to dissolve the content.

Strength	Pack size (ml)	Reconstitution volume (ml)
400 / 57 mg / 5ml	70	61

1. **Description:**

   a) Dry powder-
   Take a bottle open it on clean butter paper and observe visually against black background.
   Check the Physical aspects - Colour, lumps, presence of foreign matter etc. and record the observations.

   b) Reconstituted suspension-
   Transfer the sample into a colourless test tube having a inside diameter of 15-25 mm. Make a suspension and observe against a white background for colour and black background for clarity in diffused daylight. Preserve the sample for pH and odour test of suspension.

   Record the observations.

2. **Mean mass:**

   Select 5 containers at random. Weigh the contents of 5 containers and note down the weight in grams up to four decimals. Determine the average mass.

3. **Uniformity of weight (mass) of delivered doses from multidose containers:**

   Weigh individually 20 doses taken at random from one or more containers and determine the individual and average masses.

   Not more than 2 of the individual masses deviate from the average mass by more than 10 per cent and none deviates by more than 20 per cent

4. **pH of the suspension:**

   Adjust the temperature of sample (reconstituted suspension) under test to 25°C ± 2°C.

   Wash the electrode with purified water and blot dry. Immerse the electrode in the sample under test and measure the pH.

   Note the value and report the results.

5. **Water (By Karl Fischer method):**

Transfer an accurately weighed quantity of about 0.5 grams of sample (Dry powder) to the titration flask containing 30ml of anhydrous methanol.

Allow it to disperse for few minutes by stirring. Start the titration with Karl Fischer reagent and continue till the end point is reached. Note down the titer value (V).

Calculate the percent water content using the following formula.

$$\% \text{ Water content} = \frac{\text{Titer value (V) X KF factor X 100}}{\text{Weight of sample taken in mg}}$$

6. **Microbiological quality:**

Refer standard operating procedure for microbiological quality, SOP:QCMB:018

7. **Reconstitution time:**

Select one bottle randomly and tap the bottle lightly to loosen powder. Add half of the specified ml of water and shake well for 1 minute to hydrate the blend. Add rest of the quantity of water and shake well on its longitudinal axis (180°) to form uniform suspension. After interval of 1 minute, open the bottle & physically observe the suspension. Note down the time to form Uniform suspension with out any un-wet particles left.

6.2.1.P.7 Container Closure System (Placebo)

The container closure system for the placebo is the same as the test product.

Primary packaging: HDPE bottle with 28mm polypropylene round CRC cap containing 14g of powder for reconstitution to 70ml.

Secondary packaging: In carton with a 5ml polystyrene syringe dosing device.

6.2.1.P.8 Stability (Placebo)

A provisional 24 months shelf life has been assigned for the placebo product; this is based on the extrapolation of stability data of the test product in view that both the active and placebo formulations compromise the same excipients.

As per the active, the storage conditions for the placebo formulations will be:

Dry powder: This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

After reconstitution: Store in a refrigerator between 2°C to 8°C in the container supplied and use within 7 days.

On-going stability study on the placebo product will also be carried out. If results are compliant to the specifications as listed under section 6.2.1.P.5.1 at 18 and 24 months time points, this provisional 24 months shelf-life will be extended accordingly.

Packaging and labelling

Mawdsley-Brooks & Company Limited (MIA(IMP) 741) is responsible for the packaging and labelling of the test products and placebo comparators in a blinded manner. They are also responsible for the batch released and final QP certification of the test products and placebo comparators.

70ml Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension

- Commercial label on the HDPE bottle is removed.
- Each bottle is labelled with a blinded Annex 13 label
- Each Annex 13 labelled bottle is placed in an unbranded secondary carton with Annex 13 labelling.
- A 5ml polystyrene syringe dosing device is included in each carton.

Placebo

- Each bottle is labelled with a blinded Annex 13 label.
- Each Annex 13 labelled bottle is placed in an unbranded secondary carton with Annex 13 labelling.
- A 5ml polystyrene syringe dosing device is included in each carton.

Manufacturing site: Unit 22, Quest Park
Wheatley Hall Road
Doncaster
DN2 4LT
UK

Appendix 4 - MIA(IMP) licence – Mawdsley-Brooks & Company Limited

Appendix 1

Safeguarding public health

MHRA

Head Of Regulatory Affairs
BROWN & BURK UK LIMITED
5 MARRYAT CLOSE
HOUNSLOW
TW4 5DQ
UNITED KINGDOM

16/08/2012

Dear Head Of Regulatory Affairs,

GRANT / RENEWAL OF MARKETING AUTHORISATION

Our Reference:	PL 25298/0006 - 0001
Your Reference:	25298
Product:	Co-amoxiclav 400 mg/57 mg/5 ml Sugar Free Powder for Oral Suspension
Type of Procedure:	Decentralised
Submission Type:	Initial
Submission Category:	Abridged
EU Procedure Number (if applicable):	PT/H/603/02/DC

The Licensing Authority agrees to the grant or renewal of the marketing authorisation for the above submission on the basis of the data provided. This includes any replacement and amendment of the original dossier.

In line with Article 23a of Directive 2001/83/EC as amended, the Marketing Authorisation Holder should submit notification of the actual date of marketing of the product to the Competent Authority.
This notification should be provided by email to the following address: sunsetclause@mhra.gsi.gov.uk.

The formal documents are enclosed. These constitute evidence of authorisation. If you consider them to contain information that is incorrect or not in accordance with the dossier, please return immediately indicating any errors.

All Marketing Authorisations are subject to standard provisions contained in current medicines regulations full details of which are published on the MHRA website:
http://www.mhra.gov.uk/mhra/marketingauthorisationprovisions
Yours sincerely,

Pratibha Madan

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

An executive agency of the Department of Health

The Medicines for Human Use (Marketing Authorisations etc.) Regulations, SI 1994/3144, as amended.

GRANT / RENEWAL OF MARKETING AUTHORISATION

Product:	PL 25298/0006 - Co-amoxiclav 400 mg/57 mg/5 ml Sugar Free Powder for Oral Suspension
Submission Type:	Initial
Granted to:	BROWN & BURK UK LIMITED 5 MARRYAT CLOSE HOUNSLOW TW4 5DQ UNITED KINGDOM

This Marketing Authorisation, under the above reference number is hereby granted / renewed in respect of the product named above. The Summary of Product Characteristics of the product is set out in the attached document.

The application is subject to the further provisions set out or referred to in the above Regulations.

This Marketing Authorisation, as now granted / renewed, unless previously revoked, will continue in force until the expiry date (if applicable) given below.

Grant Date:	16/08/2012
Date of Expiry:	20/06/2017

Pratibha Madan
A person authorised to sign on behalf of the Secretary of State for Health

Appendix 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-amoxiclav 400 mg/57 mg/5 mL Sugar Free Powder for Oral Suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Co-amoxiclav Sugar Free Suspension Each 5ml of reconstituted suspension contains 400 mg amoxicillin (as amoxicillin trihydrate) and 57 mg clavulanic acid (as potassium clavulanate).

Excipients:

Co-amoxiclav contains 2.5 mg of aspartame (E951) per ml.

3 PHARMACEUTICAL FORM

Powder for oral suspension.

White to off-white powder which on reconstitution with water gives white to off-white suspension with fruity aromatic odor

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-amoxiclav is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis

- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

White to off-white powder which on reconstitution with water gives white to off-white suspension with fruity aromatic odor

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Co-amoxiclav that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Co-amoxiclav (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of Co-amoxiclav provides a total daily dose of 1750 mg amoxicillin/ 250 mg clavulanic acid with twice daily dosing and 2625 mg amoxicillin/375 mg clavulanic acid with three times daily dosing, when administered as recommended below. For children < 40 kg, this formulation of Augmentin provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Co-amoxiclav is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg

Recommended doses:

- standard dose: (for all indications) 875 mg/125 mg two times a day;
- higher dose - (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875 mg/125 mg three times a day.

Children < 40 kg

Children may be treated with Co-amoxiclav tablets, suspensions or paediatric sachets.

Recommended doses:

- 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses;
- up to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

No clinical data are available for Co-amoxiclav 7:1 formulations regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years

There are no clinical data for Co-amoxiclav 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly

No dose adjustment is considered necessary.

Renal impairment

No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

In patients with creatinine clearance less than 30 ml/min, the use of Co-amoxiclav presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration

Co-amoxiclav is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Therapy can be started parenterally according to the SmPC of the IV-formulation and continued with an oral preparation.

Shake to loosen powder, add water as directed, invert and shake.
Shake the bottle before each dose (see section 6.6 and 12).

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s), consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Co-amoxiclav is not suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant S. pneumoniae.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustulae may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires Co-amoxiclav discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, Co-amoxiclav should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Co-amoxiclav may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non- *Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

Co-amoxiclav contains 2.5 mg of aspartame (E951) per ml, a source of phenylalanine.

This medicine should be used with caution in patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

4.6 Pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥ 1/10)

Common (≥ 1/100 to <1/10)

Uncommon (≥ 1/1,000 to <1/100)

Rare (≥ 1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known

Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Tooth discolouration[11]	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders [7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known

Renal and urinary disorders

Interstitial nephritis	Not known
Crystalluria[8]	Not known

[1] See section 4.4

[2] See section 4.4

[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking Co-amoxiclav at the start of a meal.

[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)

[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.

[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).

[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).

[8] See section 4.9

[9] See section 4.3

[10] See section 4.4

[11] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4)

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mechanism

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

PK/PD relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

• Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility Breakpoints (μg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus [2]	≤ 2	-	> 2
Coagulase-negative staphylococci [2]	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8
Streptococcus A, B, C, G[5]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤ 0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8

Gram-negative Anaerobes[1]	≤ 4	8	> 8
Gram-positive Anaerobes[1]	≤ 4	8	> 8
Non-species related breakpoints[1]	≤ 2	4-8	> 8

[1] The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.

[2] The reported values are Oxacillin concentrations.

[3] Breakpoint values in the table are based on Ampicillin breakpoints.

[4] The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.

[5] Breakpoint values in the table are based on Benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Gardnerella vaginalis* *Staphylococcus aureus (* methicillin-susceptible) *Streptococcus agalactiae*

Streptococcus pneumoniae[1]
Streptococcus pyogenes and other beta-haemolytic streptococci
Streptococcus viridans group
Aerobic Gram-negative micro-organisms
Capnocytophaga spp.
Eikenella corrodens
Haemophilus influenzae[2]
Moraxella catarrhalis
Pasteurella multocida
Anaerobic micro-organisms
Bacteroides fragilis
Fusobacterium nucleatum
Prevotella spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Enterococcus faecium $
Aerobic Gram-negative micro-organisms
Escherichia coli

Klebsiella oxytoca *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydophila pneumoniae*

Chlamydophila psittaci *Coxiella burnetti* *Mycoplasma pneumoniae*
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1]*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (875 mg/125 mg tablets given twice daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0\text{-}24h)}$ (µg.h/ml)	T 1/2 (h)

Amoxicillin					
AMX/CA 875 mg/125 mg	875	11.64 ± 2.78	1.50 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA 875 mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12

AMX – amoxicillin, CA – clavulanic acid

*Median (range)

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and nonrenal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Co-amoxiclav 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with Co-amoxiclav or its components.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicon Dioxide (E551)

Aspartame (E951)

Succinic acid (E363)

Xanthan Gum (E415)

Hypromellose (E464)

Colloidal anhydrous silica (E551)

Raspberry Flavour [Acacia gum (E414), Nature identical flavouring substance, Propylene glycol (E1520), Artificial flavouring substance and Flavouring preparation]

Orange Flavour [Acacia gum (E414), Flavouring preparation and Butylated hydroxyanisole (E320)]

Golden Caramel [Maltodextrin, Triethyl Citrate (E1505), Artificial Flavours and Acetic acid (E260)]

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

Dry powder: 2 Years

Reconstituted suspension: 7 days, when stored between 2°C to 8°C

6.4 Special precautions for storage

Dry powder: This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

After reconstitution: Store in a refrigerator between 2°C to 8°C in the container supplied and use within 7 days.

6.5 Nature and contents of container

Presentation 1: 5ml polystyrene syringe dosing device supplied in carton

Presentation 2: No syringe dosing device supplied in carton

HDPE bottle with 28mm polypropylene round CRC cap containing 6g, 12g, 14g and 20g of powder for reconstitution to 30ml, 60ml, 70ml and 100ml respectively.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

White to off-white powder which on reconstitution with water gives white to off-white suspension with fruity aromatic odor

Check cap seal is intact before using. Shake bottle to loosen powder. Add volume of water (as indicated below) invert and shake well.

Volume of water to be added at reconstitution (ml)	Final volume of reconstituted oral suspension (ml)
25 ml	30 ml
56 ml	60 ml
61 ml	70 ml
87 ml	100 ml

Any unused medicinal product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Brown & Burk UK Limited
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/08/2012

10 DATE OF REVISION OF THE TEXT

16/08/2012

Appendix 3

Safeguarding public health

MHRA

RESTRICTED – COMMERCIAL
Mr S M Mudda
MICRO LABS LIMITED
16 VEERASANDRA INDUSTRIAL AREA
ANEKAL TALUK
BANGALORE
KARNATAKA
IN-560 100
INDIA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

An executive agency of the Department of Health

Safeguarding public health

Certificate No: UK GMP 22481 Insp GMP 22481/366976-0003

Medicines and Healthcare products Regulatory Agency

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC.

The competent authority of the United Kingdom confirms the following:

The manufacturer	MICRO LABS LIMITED
Site address	16 VEERASANDRA INDUSTRIAL AREA ANEKAL TALUK BANGALORE KARNATAKA IN-560 100 INDIA

Has been inspected in connection with marketing authorisation(s) listing manufacturers located outside of the European Economic Area in accordance with Art.111(4) of Directive 2001/83/EC transposed in the following national legislation: Regulation 3(a) of the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations (SI 2005/2789) and Section 19(3) of the Medicines Act 1968 as amended.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 27/02/2013, it is considered that it complies with the principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, after which time the issuing authority should be consulted.

The authenticity of this certificate may be verified with the issuing authority.

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

MHRA

Part 2

Human Medicinal Products

1. MANUFACTURING OPERATIONS			
1.1	**Sterile products**		
	1.1.1	*Aseptically prepared (list of dosage forms)*	
		1.1.1.1 Large volume liquids	Not Authorised
		1.1.1.2 Lyophilisates	Not Authorised
		1.1.1.3 Semi-solids	Not Authorised
		1.1.1.4 Small volume liquids	Not Authorised
		1.1.1.5 Solids and implants	Not Authorised
		1.1.1.6 Other aseptically prepared products	Not Authorised
	1.1.2	*Terminally sterilised (list of dosage forms)*	
		1.1.2.1 Large volume liquids	Not Authorised
		1.1.2.2 Semi-solids	Not Authorised
		1.1.2.3 Small volume liquids	Not Authorised
		1.1.2.4 Solids and implants	Not Authorised
		1.1.2.5 Other terminally sterilised prepared products	Not Authorised
	1.1.3	Batch certification only	Not Authorised

1.2	**Non-sterile products**		
	1.2.1	*Non-sterile products (list of dosage forms)*	
		1.2.1.1 Capsules, hard shell	Authorised
		1.2.1.2 Capsules, soft shell	Not Authorised
		1.2.1.3 Chewing gums	Not Authorised
		1.2.1.4 Impregnated matrices	Not Authorised
		1.2.1.5 Liquids for external use	Not Authorised
		1.2.1.6 Liquids for internal use	Not Authorised
		1.2.1.7 Medicinal gases	Not Authorised
		1.2.1.8 Other solid dosage forms	Not Authorised
		1.2.1.9 Pressurised preparations	Not Authorised
		1.2.1.10 Radionuclide generators	Not Authorised
		1.2.1.11 Semi-solids	Not Authorised
		1.2.1.12 Suppositories	Not Authorised
		1.2.1.13 Tablets	Authorised
		1.2.1.14 Transdermal patches	Not Authorised
		1.2.1.15 Intraruminal devices	Not Authorised
		1.2.1.16 Veterinary premixes	Not Authorised
		1.2.1.17 Other non-sterile medicinal product *Oral powder for reconstruction*	Authorised
	1.2.2	*Batch certification only*	Not Authorised
1.3	**Biological medicinal products**		
	1.3.1	*Biological medicinal products*	
		1.3.1.1 Blood products	Not Authorised
		1.3.1.2 Immunological products	Not Authorised
		1.3.1.3 Cell therapy products	Not Authorised
		1.3.1.4 Gene therapy products	Not Authorised
		1.3.1.5 Biotechnology products	Not Authorised
		1.3.1.6 Human or animal extracted products	Not Authorised
		1.3.1.7 Other biological medicinal products	Not Authorised

	1.3.2	*Batch certification only (list of product types)*	
		1.3.2.1 Blood products	Not Authorised
		1.3.2.2 Immunological products	Not Authorised
		1.3.2.3 Cell therapy products	Not Authorised
		1.3.2.4 Gene therapy products	Not Authorised
		1.3.2.5 Biotechnology products	Not Authorised
		1.3.2.6 Human or animal extracted products	Not Authorised
		1.3.2.7 Other biological medicinal products	Not Authorised
1.4	**Other products or manufacturing activity**		
	1.4.1	*Manufacture of:*	
		1.4.1.1 Herbal products	Not Authorised
		1.4.1.2 Homoeopathic products	Not Authorised
		1.4.1.3 Biological active starting materials	Not Authorised
		1.4.1.4 Other	Not Authorised
	1.4.2	*Sterilisation of active substances/excipients/finished product:*	
		1.4.2.1 Filtration	Not Authorised
		1.4.2.2 Dry heat	Not Authorised
		1.4.2.3 Moist heat	Not Authorised
		1.4.2.4 Chemical	Not Authorised
		1.4.2.5 Gamma irradiation	Not Authorised
		1.4.2.6 Electron beam	Not Authorised
	1.4.3	Other	Not Authorised

1.5	**Packaging only**		
	1.5.1	*Primary packaging*	
		1.5.1.1 Capsules, hard shell	Not Authorised
		1.5.1.2 Capsules, soft shell	Not Authorised
		1.5.1.3 Chewing gums	Not Authorised
		1.5.1.4 Impregnated matrices	Not Authorised
		1.5.1.5 Liquids for external use	Not Authorised
		1.5.1.6 Liquids for internal use	Not Authorised
		1.5.1.7 Medicinal gases	Not Authorised
		1.5.1.8 Other solid dosage forms	Not Authorised
		1.5.1.9 Pressurised preparations	Not Authorised
		1.5.1.10 Radionuclide generators	Not Authorised
		1.5.1.11 Semi-solids	Not Authorised
		1.5.1.12 Suppositories	Not Authorised
		1.5.1.13 Tablets	Not Authorised
		1.5.1.14 Transdermal patches	Not Authorised
		1.5.1.15 Intraruminal devices	Not Authorised
		1.5.1.16 Veterinary premixes	Not Authorised
		1.5.1.17 Other non-sterile medicinal products	Not Authorised
	1.5.2	Secondary packaging	Authorised
1.6	**Quality control testing**		
	1.6.1	Microbiological: sterility	Not Authorised
	1.6.2	Microbiological: non-sterility	Authorised
	1.6.3	Chemical/Physical	Authorised
	1.6.4	Biological	Not Authorised

2. IMPORTATION OF MEDICINAL PRODUCTS			
2.1	Quality control testing of imported medicinal products		
	2.1.1	Microbiological: sterility	Not Authorised
	2.1.2	Microbiological: non-sterility	Not Authorised
	2.1.3	Chemical/Physical	Not Authorised
	2.1.4	Biological	Not Authorised
2.2	Batch certification of imported medicinal products		
	2.2.1	*Sterile Products*	
		2.2.1.1 Aseptically prepared	Not Authorised
		2.2.1.2 Terminally sterilised	Not Authorised
	2.2.2	Non-sterile Products	Not Authorised
	2.2.3	*Biological medicinal products*	
		2.2.3.1 Blood products	Not Authorised
		2.2.3.2 Immunological product	Not Authorised
		2.2.3.3 Cell therapy products	Not Authorised
		2.2.3.4 Gene therapy products	Not Authorised
		2.2.3.5 Biotechnology products	Not Authorised
		2.2.3.6 Human or animal extracted products	Not Authorised
		2.2.3.7 Other biological medicinal products	Not Authorised
	2.2.4	*Other importation activities*	
		2.2.4.1 Radiopharmaceuticals/Radionuclide generators	Not Authorised
		2.2.4.2 Medicinal gases	Not Authorised
		2.2.4.3 Herbal products	Not Authorised
		2.2.4.4 Homoeopathic products	Not Authorised
		2.2.4.5 Biological active starting materials	Not Authorised
		2.2.4.6 Other	Not Authorised

Manufacture of active substance. Names of substances subject to inspection:

ACTIVE NAME
N/A

EXCIPIENT NAME
N/A

Any restrictions or clarifying remarks related to the scope of this certificate:

N/A

1. Building(s)/Area(s)

   N/A

2. Room(s)

   N/A

3. Line(s) Equipment(s)

   N/A

4. QC testing

   N/A

5. Medicinal Product(s)/IMP(s)

   N/A

Name of the authorised person of the Competent Authority of the United Kingdom

Norman Gray
GMP Inspector
Norman.Gray@mhra.gsi.gov.uk

Date: 16/04/2013

Appendix 4

Safeguarding public health

MHRA

Mrs Michelle Biggs
MAWDSLEY-BROOKS & COMPANY LIMITED
UNIT 3
SOUTH LANGWORTHY ROAD
PO BOX 18
SALFORD
M50 2PW
UNITED KINGDOM

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

An executive agency of the Department of Health

MIA(IMP) NUMBER: MIA(IMP) 741 Version: 7

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 1A

1. **Authorisation Number**

   MIA(IMP) Number: MIA(IMP) 741

2. **Name of Authorisation Holder**

   MAWDSLEY-BROOKS & COMPANY LIMITED

3. **Address(es) of manufacturing/importing site(s)**
   (All authorised sites should be listed if not covered by separate licences)

MHRA SITE NUMBER:	SITE NAME:	ADDRESS:
1686685	MAWDSLEY-BROOKS & COMPANY LIMITED	UNIT 22, QUEST PARK, WHEATLEY HALL ROAD, DONCASTER, DN2 4LT, UNITED KINGDOM

4. **Legally registered address of Authorisation Holder**

   UNIT 3, SOUTH LANGWORTHY ROAD, PO BOX 18, SALFORD, M50 2PW, UNITED KINGDOM

5. **Scope of authorisation and dosage forms**

   See Annex 2

6. **Legal basis of authorisation**

   See Section 1B of authorisation.

7. **Name of responsible officer of the competent authority of the member state granting the manufacturing authorisation**

   Sean Kaiser

8. **Date** 11/12/2012

SECTION 1A (continued)

9. Annexes attached

Annex 2

Optional Annexes

Annex 4 (Contract Laboratories)

Annex 5 (Name of Qualified Person)

Annex 6 (Name of Responsible Person)

Annex 8 (Manufactured/Imported products)

Annex 9 (Storage Sites)

MHRA

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 1B

1. This authorisation is granted in accordance with the provisions of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] which implement Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001.

2. It permits the authorisation holder named on page 1 of Section 1 of the authorisation to manufacture, assemble and/or import investigational medicinal products for human use in accordance with Regulation 41 of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] (as detailed in section 3 of this authorisation) and is subject to the provisions identified on page 2 of Section 1 of this authorisation.

3. In this document a Manufacturers Authorisation for Investigational Medicinal Products may be referred to as MIA(IMP) and the Medicines and Healthcare products Regulatory Agency (acting on behalf of the Licensing Authority as defined in Regulation 6 of The Human Medicines Regulations 2012 (SI 2012/1916) may be referred to as MHRA.

4. The authorisation holder must inform the MHRA, in advance, of any change to the details submitted by him and/or included in this authorisation. All changes must be approved by the MHRA to have effect. If the business should change hands, the company or person taking over the business will have to obtain a new authorisation before commencing the manufacture, assembly or importation of investigational medicinal products.

Attention is drawn to the structure of this authorisation (as detailed on page 4 of Section 1) and to its completeness in accordance with that structure. This is of particular relevance where the holder of the authorisation is using it as evidence to a third party in support of claims to carry out those operations and activities to which this authorisation applies on premises and using personnel covered by this authorisation.

SECTION 1B (continued)

5. Authorisation Structure

This authorisation is divided into three sections.

(a) Section 1 (this section) identifies the authorisation holder and the responsible officer for the issue of the authorisation. This section would not usually be replaced during routine variations of the authorisation unless the authorisation holder details are varied.

(b) Section 2 lists variations to the authorisation. A replacement section 2 will be issued each time the authorisation is varied.

(c) Section 3 contains the details relating to each site named on the authorisation. Where there is more than one site there will be more than one part to Section 3. When a variation is made to the details of a site named in Section 3 the relevant part of Section 3 will be replaced.

(d) The authorisation holder is required to attach to his authorisation any replacement pages issued by MHRA and to mark or destroy superseded pages as to render them invalid.

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6. Provisions

a) The provisions of Schedule 7 of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] shall apply to the authorisation. For manufacture and/or assembly Parts 1 and 2 of Schedule 7 apply and for importation Parts 1 and 3 of Schedule 7 apply in accordance with Regulation 40(4) of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] subject to Regulation 38(2).

MHRA

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 2

VARIATION HISTORY

This page will be amended if the licence is varied.

Date	Variation Detail
02/02/2011	Initial Application
03/02/2011	Internal variation to Site 1686685 (Unit 22, Quest Park): amend the site name, add Mrs Emma Thomson as QP & QC and delete Mr Philip Millward
11/02/2011	Internal variation to Site 1686685 (Unit 22, Quest Park): Add sections 1.1.3 (Batch cert of sterile Products), 1.2.2 (Batch cert of non Sterile Products) and 1.4.3 (Other: Batch release of herbals)
14/02/2011	Internal variation to add 2.2.1.1 to site 1686685.
31/07/2012	Variation: Add new QP Miss Jennifer Anne McLaughlin.
21/11/2012	RBI - Variation to change name of site 3163392 to MAWDSLEY-BROOKS & COMPANY LIMITED
11/12/2012	Variation - site 1686685, add Qualified Persons, Ms M C Siruffo and Dr S Yong, remove site contact Mr D Wood, add new site contact Mrs E Thomson. Add storage site 3163392.

MHRA

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 3

ANNEX 2 - SITE INFORMATION

SCOPE OF AUTHORISATION

Name and address of site:

SITE NAME:	MAWDSLEY-BROOKS & COMPANY LIMITED
ADDRESS:	UNIT 22, QUEST PARK, WHEATLEY HALL ROAD, DONCASTER, DN2 4LT, UNITED KINGDOM
MHRA SITE NUMBER:	1686685

Type of products handled

Human Investigational Medicinal Products for phase I, II, III clinical trials (optional)

Authorised operations

Manufacturing Operations of Investigational Medicinal Products (according to Part 1)	Authorised
Importation of Investigational Medicinal Products (according to Part 2)	Authorised

ANNEX 2 – SITE INFORMATION (continued)

Part 1 – MANUFACTURING OPERATIONS OF INVESTIGATIONAL MEDICINAL PRODUCTS

- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, importation, storage and distribution of specified dosage forms unless informed to the contrary;
- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;
- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

1.1	**Sterile Investigational Medicinal Products**	**Manufacture**
1.1.1	**Aseptically Prepared (list of dosage forms)**	
	1.1.1.1 Large volume liquids	Not Authorised
	1.1.1.2 Lyophilisates	Not Authorised
	1.1.1.3 Semi-solids	Not Authorised
	1.1.1.4 Small volume liquids	Not Authorised
	1.1.1.5 Solids and implants	Not Authorised
	1.1.1.6 Other aseptically prepared products	Not Authorised

1.1.2	*Terminally Sterilised*	**Manufacture**
	1.1.2.1 Large volume liquids	Not Authorised
	1.1.2.2 Semi-solids	Not Authorised
	1.1.2.3 Small volume liquids	Not Authorised
	1.1.2.4 Solids and implants	Not Authorised
	1.1.2.5 Other terminally sterilised prepared products	Not Authorised
1.1.3	***Batch certification only***	Authorised

1.2	Non-sterile investigational medicinal products	Manufacture
1.2.1	***Non-sterile products (list of dosage forms)***	
	1.2.1.1 Capsules, hard shell	Not Authorised
	1.2.1.2 Capsules, soft shell	Not Authorised
	1.2.1.3 Chewing gums	Not Authorised
	1.2.1.4 Impregnated matrices	Not Authorised
	1.2.1.5 Liquids for external use	Not Authorised
	1.2.1.6 Liquids for internal use	Not Authorised
	1.2.1.7 Medicinal gases	Not Authorised
	1.2.1.8 Other solid dosage forms	Not Authorised
	1.2.1.9 Pressurised preparations	Not Authorised
	1.2.1.10 Radionuclide generators	Not Authorised
	1.2.1.11 Semi-solids	Not Authorised
	1.2.1.12 Suppositories	Not Authorised
	1.2.1.13 Tablets	Not Authorised

	1.2.1.14 Transdermal patches	Not Authorised
	1.2.1.15 Other non-sterile medicinal products	Not Authorised
1.2.2	Batch certification only	Authorised

1.3	Biological investigational medicinal products	Manufacture
1.3.1	***Biological medicinal products (list of product types)***	
	1.3.1.1 Blood products	Not Authorised
	1.3.1.2 Immunological products	Not Authorised
	1.3.1.3 Cell therapy products	Not Authorised
	1.3.1.4 Gene therapy products	Not Authorised
	1.3.1.5 Biotechnology products	Not Authorised
	1.3.1.6 Human or animal extracted products	Not Authorised
	1.3.1.7 Other biological medicinal products	Not Authorised
1.3.2	***Batch certification only (list of product types)***	
	1.3.2.1 Blood products	Not Authorised
	1.3.2.2 Immunological products	Not Authorised
	1.3.2.3 Cell therapy products	Not Authorised
	1.3.2.4 Gene therapy products	Not Authorised
	1.3.2.5 Biotechnology products	Not Authorised
	1.3.2.6 Human or animal extracted products	Not Authorised
	1.3.2.7 Other biological medicinal products	Not Authorised

1.4	***Other investigational medicinal products or manufacturing activity*** (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials (when required by national legislation), medicinal gases, herbal or homeopathic products, bulk or total manufacturing, etc).	**Manufacture**
1.4.1	**Manufacture of:**	
	1.4.1.1 Herbal products	Not Authorised
	1.4.1.2 Homoeopathic products	Not Authorised
	1.4.1.3 Biological active starting materials	Not Authorised
	1.4.1.4 Other	Not Authorised
1.4.2	**Sterilisation of active substances/excipients/finished products:**	
	1.4.2.1 Filtration	Not Authorised
	1.4.2.2 Dry heat	Not Authorised
	1.4.2.3 Moist heat	Not Authorised
	1.4.2.4 Chemical	Not Authorised
	1.4.2.5 Gamma irradiation	Not Authorised
	1.4.2.6 Electron beam	Not Authorised
1.4.3	**Others** Batch release of Herbals	Authorised

1.5	*Packaging only*	Packaging
1.5.1	***Primary packing***	
	1.5.1.1 Capsules, hard shell	Not Authorised
	1.5.1.2 Capsules, soft shell	Not Authorised
	1.5.1.3 Chewing gums	Not Authorised
	1.5.1.4 Impregnated matrices	Not Authorised
	1.5.1.5 Liquids for external use	Not Authorised
	1.5.1.6 Liquids for internal use	Not Authorised
	1.5.1.7 Medicinal gases	Not Authorised
	1.5.1.8 Other solid dosage forms	Not Authorised
	1.5.1.9 Pressurised preparations	Not Authorised
	1.5.1.10 Radionuclide generators	Not Authorised
	1.5.1.11 Semi-solids	Not Authorised
	1.5.1.12 Suppositories	Not Authorised
	1.5.1.13 Tablets	Not Authorised
	1.5.1.14 Transdermal patches	Not Authorised
	1.5.1.15 Other non-sterile medicinal products	Not Authorised
1.5.2	**Secondary packing**	Authorised

1.6	Quality control testing	
	1.6.1 Microbiological: sterility	Not Authorised
	1.6.2 Microbiological: non-sterility	Not Authorised
	1.6.3 Chemical/Physical	Not Authorised
	1.6.4 Biological	Not Authorised

Any restrictions or clarifying remarks related to the scope of these Manufacturing operations:

ANNEX 2 – SITE INFORMATION (continued)

Part 2 – IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS

- authorised importation activities without manufacturing activity
- authorised importation activities include storage and distribution unless informed to the contrary

2.1	Quality control testing	Import
	2.1.1 Microbiological: sterility	Not Authorised
	2.1.2 Microbiological: non-sterility	Not Authorised
	2.1.3 Chemical/Physical	Not Authorised
	2.1.4 Biological	Not Authorised
2.2	**Batch certification of imported medicinal products**	
2.2.1	***Sterile Products***	
	2.2.1.1 Aseptically prepared	Authorised
	2.2.1.2 Terminally sterilised	Authorised
2.2.2	***Non-sterile products***	Authorised
2.2.3	***Biological medicinal products***	
	2.2.3.1 Blood products	Authorised
	2.2.3.2 Immunological products	Authorised
	2.2.3.3 Cell therapy products	Authorised

	2.2.3.4 Gene therapy products	Authorised
	2.2.3.5 Biotechnology products	Authorised
	2.2.3.6 Human or animal extracted products	Authorised
	2.2.3.7 Other biological medicinal products	Not Authorised
2.2.4	***Other importation activities*** (any other relevant importation activity that is not covered above e.g. importation of radiopharmaceuticals, medicinal gases, herbal or homeopathic products, etc.)	
	2.2.4.1 Radiopharmaceuticals/Radionuclide generators	Not Authorised
	2.2.4.2 Medicinal gases	Not Authorised
	2.2.4.3 Herbal products	Not Authorised
	2.2.4.4 Homoeopathic products	Not Authorised
	2.2.4.5 Biological active starting materials	Not Authorised
	2.2.4.6 Other Pi Labelling of blisters and foils, batch release of herbals.	Authorised

Any restrictions or clarifying remarks related to the scope of these importing operations:

ANNEX 5/6 – SITE INFORMATION (continued)

Personnel

Person Number	Name	Personnel Type			
		QP	TQP	PM	QC
1259637	Dr Martin Frederick Jones	Yes	No	No	No
128087	Mr Stephen T Garner	Yes	No	No	Yes
6841970	Miss Jennifer Anne McLaughlin	Yes	No	No	No
2228891	Miss Kelly Ounsley	No	No	Yes	No
126523	Mr Jeff Cox	Yes	No	No	No
119278	Mrs E Thomson	Yes	No	No	Yes
4734657	Mrs Maria Cecilia Siruffo Perez	Yes	No	No	No
623766	Dr Set Hui Yong	Yes	No	No	No

Key to Roles:

QP – Qualified Person
TQP – Transitional Qualified Person
PM – Production Manager/Supervisor
QC – Person responsible for Quality Control

ANNEX 4 – CONTRACT LABORATORIES

MHRA SITE NUMBER:	LABORATORY NAME:	ADDRESS:
5566	QUALITY CONTROL NORTH WEST	STEPPING HILL HOSPITAL, STOCKPORT, CHESHIRE, SK2 7JE, UNITED KINGDOM
12378	MINERVA SCIENTIFIC LIMITED	DELVES ROAD, HEANOR GATE, DERBYSHIRE, DE75 7SG, UNITED KINGDOM
28874	EXOVA (UK) LIMITED	LOCHEND INDUSTRIAL ESTATE, NEWBRIDGE, MIDLOTHIAN, EH28 8PL, UNITED KINGDOM

ANNEX 9 – STORAGE SITES

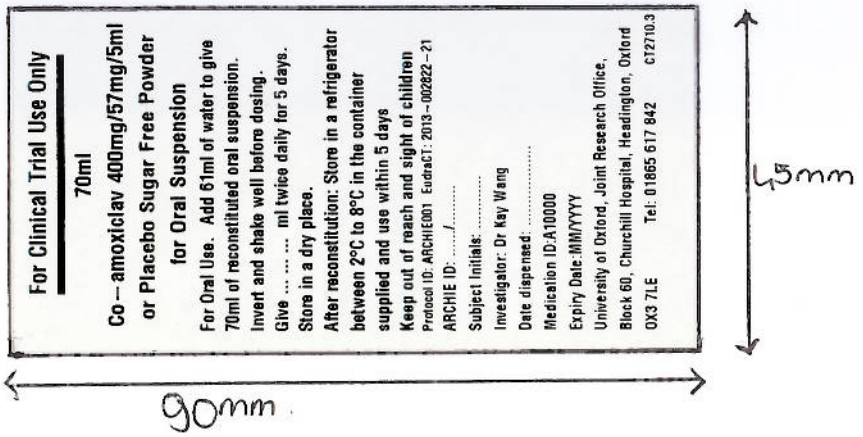
MHRA SITE NUMBER:	SITE NAME:	ADDRESS:
1686685	MAWDSLEY-BROOKS & COMPANY LIMITED	UNIT 22, QUEST PARK, WHEATLEY HALL ROAD, DONCASTER, DN2 4LT, UNITED KINGDOM
3163392	MAWDSLEY-BROOKS & COMPANY LIMITED	QUEST 90, QUEST PARK, WHEATLEY HALL ROAD, DONCASTER, SOUTH YORKSHIRE, DN2 4LT, UNITED KINGDOM
89833	MAWDSLEY BROOKS & COMPANY LIMITED	FINGLE DRIVE, STONEBRIDGE, MILTON KEYNES, BUCKINGHAMSHIRE, MK13 0DN, UNITED KINGDOM
91444	MAWDSLEYS (YORKSHIRE) LIMITED	Parkway Drive, Unit 7, Parkway One Business Centre, Sheffield, Yorkshire, S9 4WU, UNITED KINGDOM
93570	MAWDSLEY BROOKS & COMPANY LIMITED	UNIT 3, SOUTH LANGWORTHY ROAD, SALFORD, M50 2PW, UNITED KINGDOM

Mawdsleys

Standard Operating Procedure Form
Clinical Services - Quest Park

TITLE:	QF304b – C/T Label Approval & Checklist

Trial Identifier: **ACE**	Created by: **Mawdsleys for Mawdsleys application**
Label Code & Version Number: **CT2710.3**	Label Size: **BLA33**
Reason for Revision: **Removed 'below 25°C' from storage instructions as per Tricia Carver request**	
Contents Type: **Full Annex 13 Label or equivalent (Blinded)**	Label Type: **Black Out**
Label applied to: **Secondary Packaging**	Packaging type: **Carton**
Language: **English**	Country: **UK**
Label Placement: **Apply to the front face, aligned with top left corner.**	
Label Variable field setup: **Expiry date variable field is set to not change once data is inputted. Kit No: variable field is set up to increase sequentially after every second label printed. One kit number label is for labelling the product and one for Mawdsley's retention.**	



Comments:		
Created by: **Amie Lake**	Signature: Amie	Date: **02 June 2014**

1. Mawdsleys Authorisation

Name: S. Litman	Signature:	Date: 3 June 2014

2. Client review and Authorisation

Comments:

Label Submitted as part of Initial Application to licensing authority: ☐
Label Submitted as part of an amendment to the licensing authority: ☐

Client Authorisation:

Name:	Signature:	Date:

3. Mawdsleys Final Approval

Name:	Signature:	Date:

Written by: Kelly Ounsley Date: 24-May-2013	Approved by: Date: 28th May 2013

REVISION HISTORY

Version	Revision	Supersedes
1.0	Initial version	New
2.0	Revised to incorporate the Label Approval Checklist QF304c and to add drop down lists	1.0
3.0	Revised due to the sequencing of numbers being incorrect	2.0
4.0	Addition of System Update Section.	3.0
5.0	General review and streamline of information within the form	4.0

Mawdsleys

Standard Operating Procedure Form
Clinical Services - Quest Park

TITLE:	QF304b – C/T Label Approval & Checklist

Label Information Checklist

Label Code:	CT2710.3	Version Number:	3.0

1. Label Creation and Authorisation

	Information		QP Checked by
√KL	1	Check created label against Annexe 13	
√KL	2	Check information on label against 'C/T Label Creation Questionnaire (QF304a)' if applicable	
√KL	3	Check code on label is the same as code on the form	
√KL	4	Check label size, packaging and type is correct	
√KL	5	Check Trial Reference stated on label	
N/A	6	Check 'Mawdsleys 3 digit trial identifier'	N/A
√KL	7	Check label placement against 'C/T Label Creation Questionnaire (QF304a)' if applicable	
√KL	8	Check the country of destination is correct	
	9	Complete details in section 1 'Mawdsleys Authorisation'	
N/A	10	If translated, check the 'Translation Certificate'	N/A

Comments:

2. Client Review and Authorisation

** The label is supplied to the client for review and authorisation.

3. Mawdsleys Final Approval

Information (If applicable, *check information against the label text submitted with the Clinical Trial Application)*		QP Checked by
1	Product, Strength and form	
2	EudraCT Number	
3	Protocol Number/Trial Reference Code	
4	Sponsor Details	
5	Route of Administration	
6	Storage Conditions	

Comments:

SYSTEM UPDATE *(To be completed by Clinical Trials Staff)*	**Coordinated by:**	**Date:**	
Electronic label transferred to live file		Superseded label transferred to archive file	√KL 2-6-14
Label & Leaflet Codes (QF304d)			

Written by: Kelly Ounsley Date: 24-May-2013	Approved by: Date: 28th May 2013

REVISION HISTORY

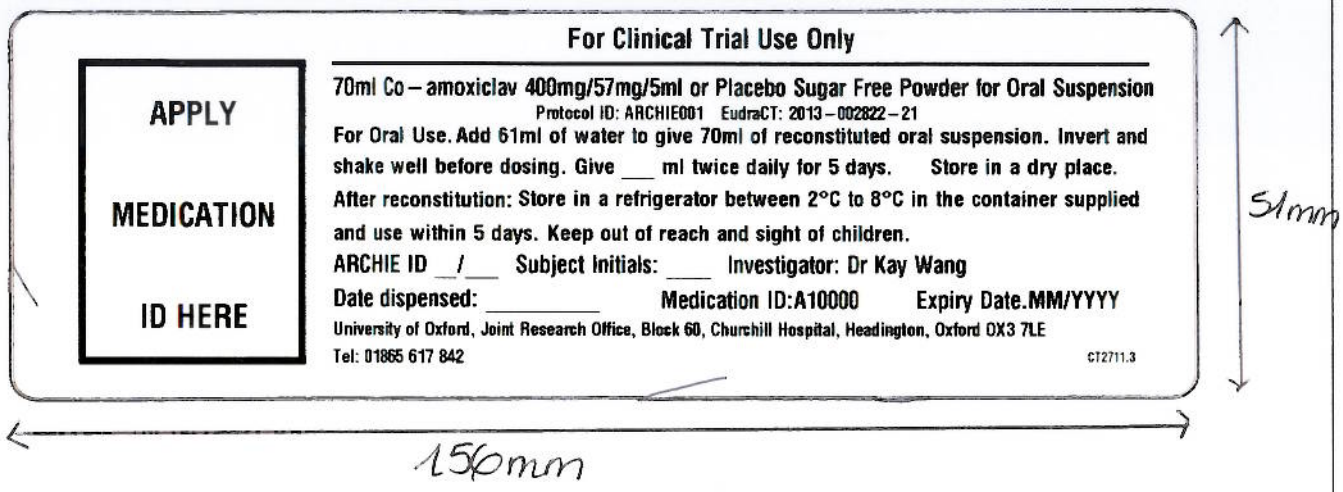
Version	Revision	Supersedes
1.0	Initial version	New
2.0	Revised to incorporate the Label Approval Checklist QF304c and to add drop down lists	1.0
3.0	Revised due to the sequencing of numbers being incorrect	2.0
4.0	Addition of System Update Section.	3.0
5.0	General review and streamline of information within the form	4.0

Mawdsleys

Standard Operating Procedure Form
Clinical Services - Quest Park

TITLE:	QF304b – C/T Label Approval & Checklist

Trial Identifier: **ACE**	Created by: **Mawdsleys for Mawdsleys application**
Label Code & Version Number: **CT2711.3**	Label Size: **BLA80**
Reason for Revision: **Removal of 'below 25°C' from storage instructions as per Tricia Carver request**	
Contents Type: **Full Annex 13 Label or equivalent (Blinded)**	Label Type: **Black Out**
Label applied to: **Primary Packaging**	Packaging type: **Bottle**
Language: **English**	Country: **UK**
Label Placement: **Apply over the existing label ensuring label edges meet or overlap.**	
Label Variable field setup: **Expiry date variable field is set to not change once data is inputted. Medication ID variable field is set up to increase sequentially after every second label printed. One medication ID label is for labelling the product and one for Mawdsley's retention.**	



Comments:		
Created by: **Amie Lake**	Signature:	Date: **02 June 2014**

1. Mawdsleys Authorisation

Name: S. FAIRBAIRN	Signature:	Date: 03 JUNE 2014

2. Client review and Authorisation

Comments:

Label Submitted as part of Initial Application to licensing authority: ☐
Label Submitted as part of an amendment to the licensing authority: ☐

Client Authorisation:

Name:	Signature:	Date:

3. Mawdsleys Final Approval

Name:	Signature:	Date:

Written by: Kelly Ounsley Date: 24-May-2013	Approved by: Date: 28th May 2013

REVISION HISTORY

Version	Revision	Supersedes
1.0	Initial version	New
2.0	Revised to incorporate the Label Approval Checklist QF304c and to add drop down lists	1.0
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4.0	Addition of System Update Section.	3.0
5.0	General review and streamline of information within the form	4.0

Mawdsleys

Standard Operating Procedure Form
Clinical Services - Quest Park

TITLE:	QF304b – C/T Label Approval & Checklist

Label Information Checklist

Label Code:	CT2711.3	Version Number:	3.0

1. Label Creation and Authorisation

	Information		QP Checked by
JDL	1	Check created label against Annexe 13	
JDL	2	Check information on label against 'C/T Label Creation Questionnaire (QF304a)' if applicable	
JDL	3	Check code on label is the same as code on the form	
JDL	4	Check label size, packaging and type is correct	
JDL	5	Check Trial Reference stated on label	
N/A	6	Check 'Mawdsleys 3 digit trial identifier'	
JDL	7	Check label placement against 'C/T Label Creation Questionnaire (QF304a)' if applicable	
JDL	8	Check the country of destination is correct	
	9	Complete details in section 1 'Mawdsleys Authorisation'	
N/A	10	If translated, check the 'Translation Certificate'	N/A

Comments:

2. Client Review and Authorisation

** The label is supplied to the client for review and authorisation.

3. Mawdsleys Final Approval

	Information (If applicable, *check information against the label text submitted with the Clinical Trial Application)*	QP Checked by
1	Product, Strength and form	
2	EudraCT Number	
3	Protocol Number/Trial Reference Code	
4	Sponsor Details	
5	Route of Administration	
6	Storage Conditions	

Comments:

SYSTEM UPDATE *(To be completed by Clinical Trials Staff)*		**Coordinated by:**	**Date:**
Electronic label transferred to live file		Superseded label transferred to archive file	JDL 2.6.14
Label & Leaflet Codes (QF304d)			

Written by: Kelly Ounsley Date: 24-May-2013	Approved by: Date: 28th May 2013

REVISION HISTORY

Version	Revision	Supersedes
1.0	Initial version	New
2.0	Revised to incorporate the Label Approval Checklist QF304c and to add drop down lists	1.0
3.0	Revised due to the sequencing of numbers being incorrect	2.0
4.0	Addition of System Update Section.	3.0
5.0	General review and streamline of information within the form	4.0

10.2 Insert Safety Alert Updates

10.3 See section 2.3 working Instruction WI 01

formerly called Trial Specific Procedure TSP 01 -

Drug Handling: Delivery, Storage, Distribution and Destruction

10.3 See section 2.3 working Instruction WI 02

(Formerly called Trial Specific Procedure TSP 02 - Destruction of Returned or Unused Drugs)

10.4 Template accountability forms

Trial medication delivery contact details

Site:

Address	Address 2	Address 3	Postcode	for the attention of:
note:				

Green light / IMP Release

Study-wide checks (completed by coordinating centre)

Task	Completed (Initial)	Date achieved (DD/MM/YYYY)	Notes
Sponsor Approval		12-08-2013	
REC Favourable Opinion Letter		10/10/2013	
MHRA Approval		03/10/2013	
Batch certificate and QP release (Technical Release)			

Site-specific checks (to be completed by site)

Centre:	
Principal Investigator:	

Task	Completed (Initial)	Date achieved (DD/MM/YYYY)	Notes
Fully-executed Site Agreement			
R&D Approval Letter from Trust			
Delegation log			
Site Initiation/Training			
Receipt of Investigator Site File (ISF)			
Receipt of recruitment box			

A copy of this form must be sent to archie@phc.ox.ac.uk to request release of IMP to site, the completed original form must be filed in the ISF

Green light Release (completed by coordinating centre)

	Completed (initials)	Date achieved (DD/MM/YYYY)
Received completed site drug allocation, dispatch and receipt form		

Upon confirmation of drug delivery, the completed original form must be filed after a copy is sent to site authorising them to start recruiting.

UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

Site Drug Allocation, Dispatch and Receipt Form

Department of Primary Care Health Sciences Clinical Trial Unit (PC CTU) to Local Site

Short trial title: **The early use of Antibiotics in at Risk Children with InfluEnza (ARCHIE)**
Eudract No.: 2013-002822-21
Sponsor: University of Oxford
Chief Investigator: Kay Wang
Medication: **ARCHIE Study IMP (Co-amoxiclav 400/57 / Placebo)**
Expiry date: **xxxxxxx**

	Print name	Signature	Date
Released by:			
Checked by:			

	Print name	Signature	Date
Posted by			
Royal Mail Recorded Delivery Reference No:			

Please take a copy of this form - Original copy to be sent with IMP to site

Staple the postage receipt to the photocopy of this form – form to be kept by the ARCHIE team

	Print name	Signature	Date
Received by:			
Checked by (where possible):			

Please email the completed form to ARCHIE Study team: archie@phc.ox.ac.uk and store the original with your drug accountability documents. If IMP is damaged/ missing/ incorrect, please call the ARCHIE team on 01865 617 842 immediately.

Primary Care Clinical Trials Unit

ARCHIE

DRUG ACCOUNTABILITY LOG

Trial title:	**The early use of Antibiotics in at Risk CHildren with InfluEnza**	EudraCT number:	**2013-002822-21**
Trial Chief Investigator	**Dr Kay Wang**	Dose form and strength	**Twice daily for 5 days** **6 months to 23 months** **• 6.0 – 7.9 kg 1 ml** **• 8.0 – 10.9 kg 1.5 ml** **• 11.0 – 12.9 kg 2 ml** **2 to 6 years 2.5 ml** **7 to 12 years 5 ml**
IMP name:	**Co-amoxiclav or placebo**		
Expiry Date:			
Dispensing site:		Local Principal Investigator:	

Date	Archie ID	Medication ID	Dose	Dispensed by	Checked by	Date returned

ARCHIE – EudraCT NUMBER 2013-002822-21

Site Name: …….. **Site Number:** ……..
IMP name: Co-amoxiclav or placebo **Principal Investigator:**
Expiry :
Batch number:

Site internal Drug Receipt Log

To be used to document the drug released from pharmacy to A&E or other trial staff

Date Received	Medication ID	Received by (signature)	Date Returned	Returned by (signature)

Primary Care Clinical Trials Unit

DRUG RETURN LOG

IMP Return Log			
Trial title:	**The early use of Antibiotics in at Risk CHildren with InfluEnza**	EudraCT number:	**2013-002822-21**
IMP name:	**Co-amoxiclav or placebo**	Dose form and strength	**Twice daily for 5 days** **6 months to 23 months** **• 6.0 – 7.9 kg 1 ml** **• 8.0 – 10.9 kg 1.5 ml** **• 11.0 – 12.9 kg 2 ml** **2 to 6 years 2.5 ml** **7 to 12 years 5 ml**
Expiry:			
Trial Chief Investigator:	**Dr Kay Wang**		
Dispensing site:		Lead PI at Site:	

	To be completed by Site Staff		To be completed by PC-CTU Staff	
Medication ID	**Released by: Name, Signature and Date**	**Checked by: Name, Signature and Date**	**Received by: Name, Signature and Date**	**Checked by: Name, Signature and Date**

Primary Care Clinical Trials Unit

ARCHIE

DRUG DESTRUCTION LOG

Investigator site:		Site Lead Investigator:	
Trial Chief Investigator:	Dr Kay Wang	Trial title:	**The early use of Antibiotics in at Risk CHildren with InfluEnza**
EudraCT number:	2013-002822-21		
IMP name:	Co-amoxiclav or placebo	Dose form and strength	**Twice daily for 5 days** **6 months to 23 months** **• 6.0 – 7.9 kg 1 ml** **• 8.0 – 10.9 kg 1.5 ml** **• 11.0 – 12.9 kg 2 ml** **2 to 6 years 2.5 ml** **7 to 12 years 5 ml**
EXPIRY:			

DATE *dd/mmm/yyyy*	MEDICATION ID	Please initial to confirm destruction	Please initial to confirm destruction (optional)

To be completed by authorised site personnel on completion of destruction

I can confirm that the drug supplies as listed above have been destroyed according to GMP / GCP guidelines.

Name: ……

Signature: ……

Date: ……

10.5 Insert completed Accountability Documents

10.6 Certificate of IMP and Placebo analysis

	MICRO LABS LIMITED, VEERASANDRA
MICRO LABS	QUALITY CONTROL DEPARTMENT
	CERTIFICATE OF ANALYSIS

Product Name	**Placebo for Co-amoxiclav 400/ 57 mg/ 5mL Sugar free powder for oral suspension**	**Page No.**	**1 of 2**
Generic Name	**Placebo for Co-amoxiclav 400/ 57 mg/ 5mL Sugar free powder for oral suspension**	**BMR No.**	**BMR1:PDAHV:EU01**
Specification Reference No.	**FPS:R:PDAHV:EU01**	**Finished Product Code**	**PDAHV;A**
A.R. No.	VFP141755	Batch Size	6,500 Bottles
Batch No.	PDAHV0001	Sampled Qty.	Control sample: 25 Bottles Analysis sample: 10 Bottles
Mfg. Date	07/2014	Expiry Date	06/2016
Sampled By	Narendra	Sampled On	07/07/2014
Date of Report	16/07/2014	Release quantity	6,230 Bottles
Presentation Pack	115 cc/28mm Heavy Weight HDPE bottle (for 70 ml) with 28 mm CRC Cap.		

Test No.	Test	Results	Specifications
Initial analysis			
1	Description i) Dry powder ii) Reconstituted Suspension	 Off-white powder. Off-white suspension with fruity aromatic odour.	 White to off-white powder. White to off-white suspension with fruity aromatic odour.
2	Mean mass	14.112g	14.0 gm ± 5% (Between 13.300 g and 14.700g)
3	Uniformity of weight (mass) of delivered doses from multidose containers	- 0.7% to + 0.5%	Not more than two of the individual mass deviate from the average mass by more than 10.0 % and none deviates by more than twice the percentage (i.e. 20.0%).
4	pH	4.21	Should be between 4.0 and 6.0
5	Water content (By KF)	2%	Not more than 10%

L:004:FCA/A

MICRO LABS	**MICRO LABS LIMITED, VEERASANDRA**
	QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS

Product Name	**Placebo for Co-amoxiclav 400/ 57 mg/ 5mL Sugar free powder for oral suspension**	**Page No.**	**2 of 2**
Generic Name	**Placebo for Co-amoxiclav 400/ 57 mg/ 5mL Sugar free powder for oral suspension**	**BMR No.**	**BMR1:PDAHV:EU01**
Specification Reference No.	**FPS:R:PDAHV:EU01**	**Finished Product Code**	**PDAHV:A**
Batch No.	PDAHV0001	A.R. No.	VFP141755

Test No.	Test	Results	Specifications
6	Microbiological quality		
	A) Total Bacterial Count	< 10 cfu/g	Not more than 1000 CFU / g
	B) Total Fungal Count	< 10cfu/g	Not more than 100 CFU / g
	C) Pathogenic organisms		
	Escherichia coli	Absent/g	Should be absent /g
7	Reconstituted time	01 minute 10 seconds	Not more than 5 minutes
Reconstituted suspension after 7 days			
1	Description Reconstituted suspension	Off-white suspension with fruity aromatic odour.	White to off-white suspension with fruity aromatic odour.
2	pH of the suspension	4.15	Should be between 4.0 and 6.0

Remarks: The sample complies / ~~does not comply~~ with specifications No.: FPS:R:PDAHV:EU01 with respect to above tests.

PREPARED BY:	CHECKED BY:	APPROVED BY:
Executive-QA(Ashok)	Asst. Manager-QC(N. Subba Reddy)	HEAD OF QC(Sridhar Reddy)
DATE: 16/07/14	DATE: 16/07/14	DATE: 16/07/14

Authorised By Sign / date: 16/07/14
(Manager-QC) **(Praveen KV)**

L:004:FCA/A

10.7 Insert documentation of IMP destruction

Primary Care
Clinical Trials Unit

FILE NOTE

FILE NOTE TITLE:	Not present: Local pharmacy agreement	File note ID/No.	03
Study acronym or short title:	ARCHIE		
Investigator (Site Name):	Kay Wang (University of Oxford)		
Date:	20 October 2014		

Local pharmacy agreements are not applicable for this trial. Section 10.9 of the ARCHIE Site File will therefore remain empty.

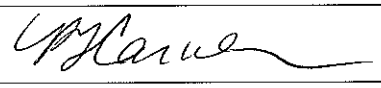
	Name (Job title)	Signature	Date
Signed (Author of file note)	Tricia Carver Senior Trial Manager		20 Oct 2014
Reviewed by (if applicable)	NA	NA	
Approved by	NA	NA	

Primary Care
Clinical Trials Unit

FILE NOTE

FILE NOTE TITLE:	Not present: Equipment records	File note ID/No.	04
Study acronym or short title:	ARCHIE		
Investigator (Site Name):	Kay Wang (University of Oxford)		
Date:	20 October 2014		

There is no equipment involved in this trial. Section 11 of the ARCHIE Site File will therefore remain empty.

	Name (Job title)	Signature	Date
Signed (Author of file note)	Tricia Carver Senior Trial Manager		20 Oct 2014
Reviewed by (if applicable)	NA	NA	
Approved by	NA	NA	

12 Monitoring and Audit Documents

Table B: PC-CTU Standard Monitoring Strategy

Time point	Details	Type of monitoring	By whom	Purpose	Outcome	Notes
Before recruitment begins	Initiation (=1st site visit)	Site / Central	TM & TT	To assess the experience of the site; including personnel, facilities, expertise and experience. Ensure site prepared all relevant documentation and supplies are in place. Train staff in protocol with emphasis on consent, eligibility and safety reporting.	Establishment of good working relationship with the site staff, emphasising the PC- CTU's role as supporters. Train staff. Flag any sites that may need extra support or monitoring in the future.	Desirable to have a named contact in each site and to meet the PI.
Ongoing	Throughout life of trial	Central	TM, TT, monitor, data manager & quality manager	Monitor that all aspects of the trial are proceeding as expected. Focused central monitoring will be carried out as identified by the risk adaption tool.	Flag sites that may require another visit.	Good communication with sites is key.
Early in recruitment	Targeted Visit #2	Site	TM	To provide follow-up training and/or support. To carry out SDV. May not be required for low risk trials. Focused site monitoring will be carried out as identified as required by the risk adaption tool.	Resolve any particular issues identified.	
At end of the trial	Close out visit (#3)	Site / Central	TM or TT	Final visit for all sites; carry out any SDV needed, collect trial supplies, documents for archiving.	Close site, thank staff, gather feedback and collect all outstanding materials.	Feedback is especially important for pilot studies.

ARCHIE Monitoring Plan

Standard monitoring will be carried out as detailed above to include;

1. Site close out visit
2. Targeted site visit, if identified as required during the course of the trial

In addition to standard monitoring, targeted monitoring as identified by the risk adaption tool will be performed to include;

The CI takes responsibility for ensuring the risk assessment is an accurate, up to date and the monitoring agreed is undertaken.

Focus	Responsibility *(use key on page 3)*	Procedure to be monitored	Monitoring procedure
Consent - Children	TT	Documentation in place.	Training records will be reviewed against delegation logs. Completed CRFs checked to ensure that only those on the delegation logs are carrying out the tasks.
Personal data – sensitive, shared with others and identifiers returned to coordinator centre	TP DM TT	OpenClinica validation and access permissions to databases Access and storage of PID	Arrangements to be reviewed and documented
Eligibility criteria – complex and other contraindications	TT CI	Enrolment of patients in study	Training logs and delegation logs to be checked against enrolment. Monitoring of any SAEs as a result of contraindication given with IMP.
Recruitment –seasonal, small pool of potential recruits and capacity issues	CI TT TS	Meeting recruitment target to ensure trial is appropriately powered	Regular review of recruitment rates during winter months. Capacity issues to be documented and appropriate action to be taken.
Randomisation - blinded	TT TS	The trial randomisation system	The baseline CRF which contain study medication allocation to be crossed checks with randomisation programme.
Intervention – IMP including delivery	TT	Training undertaken by researchers. Compliance with dosing regimen. Stock of IMP at sites	Review of training logs and parents diary. Review of medication stock.

Safety reporting – directly into OpenClinica	TT	Additional communication option for sites to use OpenClinica if they have access to report SAEs.	Documentation detailing validation of email notification when SAE received via OpenClinica.
Lab - data	TS TT	Receipt of data regarding Flu swabs	Documentation detailing data management checks in place for completeness and accuracy with data monitoring plan.
Lab - reporting	TT	Throat swab results	Regular review of collection of throat swabs in CRFs and reports of *C. diphtheriae*
Blinding / Masking – 24 hour unblinding not available	TT DSMC	Unblinding process in the case of emergency	Review of SAE reports
Endpoints – no objective measures	CI TS	Clinical deterioration has a subjective element within the primary objective	Documentation detailing the action taken to account for this in the statistical analysis plan.
Follow up - long	TT TS	Dropout rate at follow up	Regular review of collection of throat swabs and monitor number of recruits at secondary care sites.
Data - other	TT	Diaries being returned in the post	Review of return rates.
Archiving – extended period	TM	Archiving	Regular review of TMF during trial and appropriate archiving at end following SOPs.
External vendor	TT	Courier for delivery of IMP	Review of approvals in place in order to release green light release form. Complication to be documented.
Disaster recovery – special considerations	TT TP	Loss of server to trial IT systems	Documentations of systems validation and regular monitoring of systems.
Training – remote initiation	TT	Activating sites remotely	Review of approvals in place in order to release green light release form. Training records will be reviewed.
Unusual data patterns	QA	Regular queries will be run on the clinical dataset to identify sites with: • High number of ineligible patients	Reports detailing the listed metrics by site should be produced by the QA team. A copy will be forwarded to the sponsor office. If there is any

		• High/low recruitment rate • Number of SAEs • High number of data queries • High /low time for data entry • High /low time for query resolution • Unexpected data variability / uniformity • High number of protocol deviations • High staff turnover • Patient complaints received.	cause for concern by central monitoring, further action will be taken.

Agreed by:

Assessor for Risk Assessment and Monitoring Plan	Trial Manager
Name: Clare Riddle	Name: Tricia Carver
Signature: Clare Riddle	Signature: Tricia Carver
Date: 02-SEPT-2014	Date: 8 Sept 2014
Chief Investigator	**Head of Trials**
Name: Kay Wang	Name: Maria Breen
Signature: KW	Signature:
Date: 02-SEPT-2014	Date: 14 Sept 2014.

12.3 Monitoring reports (monitoring visits/remote checks)

12.4 Monitoring correspondence (including phone, follow-up letters etc)

12.5 Site closure report

Section 13 Records of all significant telephone conversations and emails relating to the study

14.1 Please refer to Work Instruction 3a (see Section 2. 2.3 Working Instructions)

14.2 Copies of broken blinds (at the end of the trial)

ARCHIE

TM119-A ADVERSE EVENT (AE) REPORT LOG

Study Title: ARCHIE (The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care)	Site Name:
Principal Investigator: Dr Kay Wang	

PLEASE READ INSTRUCTIONS BEFORE COMPLETING

PARTICIPANT ID: _ _ _ / _ _ _ _

Adverse Event (diagnosis [if known] or signs/symptoms)	**Date of Onset** *dd / mm / yyyy*	**Outcome** [1-6]	**Severity** [1-3]	**Relationship to study drug (must be assessed by medically qualified individual)** [1-4]	**Date of Resolution** *dd / mm / yyyy*	**Is the Adverse Event serious?** [1-6]	**Name of person entering AE to log and date entered**	**AE details entered into clinical study database (tick when entered)**	**Adverse Event ID** *(to be completed by coordinating centre or site)*
	/ /				/ /				01
	/ /				/ /				02
	/ /				/ /				03

If your answer is anything other than 1 to 'Is the Adverse Event serious?'.
PLEASE COMPLETE A SERIOUS ADVERSE EVENT REPORT FORM AND SEND TO COORDINATING CENTRE WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT

Key

Outcome - 1 = resolved, 2 = resolving, 3 = not resolved, 4 = resolving with sequelae, 5 = unknown, 6 = Fatal

Severity - 1 = Mild, 2 = Moderate, 3 = Severe

Relationship to Drug - 1 = not related, 2 = possibly related, 3 = probably related, 4 = definitely related

Is the adverse event serious?

1 = NO, 2 = results in death, 3 = is life-threatening, 4 = requires inpatient hospitalisation or prolongation of existing hospitalisation, 5 = results in persistent or significant disability / incapacity, 6 = is a congenital anomaly / birth defect, 7 = other important medical event

PARTICIPANT ID: _ _ _ / _ _ _ _									
Adverse Event (diagnosis [if known] or signs/symptoms)	**Date of Onset** *dd / mm / yyyy*	**Outcome** [1-6]	**Severity** [1-3]	**Relationship to study drug (must be assessed by medically qualified individual)** [1-4]	**Date of Resolution** *dd / mm / yyyy*	**Is the Adverse Event serious?** [1-6]	**Name of person entering AE to log and date entered**	**AE details entered into clinical study database (tick when entered)**	**Adverse Event ID** *(to be completed by coordinating centre or site)*
	/ /				/ /				04
	/ /				/ /				05
	/ /				/ /				06
	/ /				/ /				07
	/ /				/ /				08

Internal Use Only
SAE Identifier: _____

Serious Adverse Event Report Form (CTIMP)

Form completion instructions overleaf

1. Report type *(tick one)* Initial report ☐ Follow-up information ☐

2. Site name: _____

3. Participant details

ARCHIE ID: ☐☐☐/☐☐☐☐

Date of birth: DD/MM/YY

Sex: Male ☐ Female ☐

Weight: ☐☐☐☐ *g* OR ☐☐.☐ *kg*

(delete as applicable)

4. ADVERSE EVENT DESCRIPTION:

(Please record diagnosis if known, an account of the event including signs and symptoms if diagnosis not known, any interventions given to manage the event including dates for these and if event fatal, cause of death if known):

_____

_____

_____

_____

_____

_____

5. Start date and time of SAE: DD/MM/YY hh:mm

6. Stop date and time of SAE: DD/MM/YY hh:mm Or ongoing ☐

7. Date and time site became aware of SAE: DD/MM/YY hh:mm

Please complete and send this form immediately, no later than 24 hours after becoming aware of the SAE.

PLEASE FAX / EMAIL FORM TO: archie@phc.ox.ac.uk

01865 617939

General Instructions

- Complete the SAE Reporting Form as soon as possible but no later than 24 hours after becoming aware of the event.
- Refer to the trial protocol for definitions of Adverse Events (AEs), Adverse Reactions (ARs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events (SUSARs).
- Use a black ball point pen to complete the form.
- Fax / Email the completed form to the Trial Co-ordinating centre: 01865 617939 / archie@phc.ox.ac.uk
  Expect confirmation of receipt from the ARCHIE Trial team
- File a copy of the completed SAE Reporting Form in your Investigator Site File / Study File.
- If you have any questions regarding the classification of an adverse event or form completion then please call your Trial Manager: Tel: 01865 617842 / email: archie@phc.ox.ac.uk
- Guidelines are not provided for data fields which are self-explanatory.
- Ensure ALL details of the SAE are documented in the participant's medical records including the Investigator's assessment of causality, which the study physician must document in the medical records.
- Record 'NK' for any data that is not known.
- Record all times as 24 hour clock

Page 1

Q1. If this is the first time the SAE has been reported then please tick "initial". If you are submitting new, updated or corrected information for a previously reported SAE then please tick "follow-up information".

Q3. Record the unique trial number assigned to the participant.
Enter the participant's weight in grams **OR** kilograms and delete the unit which is not applicable.

Q5. Enter date and time that the adverse event became serious.

Q6. Enter date and time that the adverse event stopped being serious (for example, if a participant has a life-threatening condition which was resolved by surgery then the date and time for end of surgery would be entered).

Q7. Enter the time and date that a member of the site trial/study team became aware of the SAE.

Internal Use Only
SAE Identifier: _____

ARCHIE ID: [ ][ ][ ]/[ ][ ][ ][ ]

Serious Adverse Event Report Form

Form completion instructions overleaf

8. Please record severity of event: *(tick one box only)*

Mild ☐ Moderate ☐ Severe ☐

9. Reason this event is classified as Serious: *(tick one box only)*

Fatal ☐ Life threatening ☐

Requiring/prolonging hospitalisation ☐ Congenital anomaly/birth defect ☐

Significant disability/incapacity ☐ Other important medical event ☐

10. Relevant medical history: *(including co-existing medical conditions, allergies or similar experiences)*

11. Laboratory results relevant to the SAE: (*Please give details of relevant results, dates and reference ranges in the space below or attach a printout with these details highlighted and patient identifiable information obscured)*

12. Specify the study drug details below:

Study drug name	Dose	Frequency	Route	Date started	If discontinued, date stopped
				D D / M M / Y Y	D D / M M / Y Y
				D D / M M / Y Y	D D / M M / Y Y

Did the event resolve after stopping study drug? Yes ☐ No ☐ N/A ☐

Did the event reappear after reintroduction? Yes ☐ No ☐ N/A ☐

Action taken with study drug:

None ☐ Discontinued temporarily ☐

Dose reduced ☐ Discontinued ☐

Dose temporarily reduced ☐

Page 2

Q8. Choose **one** of the severity options to describe the intensity of the event.

Q9. Choose **one** of the reasons why the adverse event has been classified as serious. If there is more than one reason which applies then choose the more/most significant one and document other reason(s) in the AE description.

Q10. Provide a full description of any medical history which could be relevant to this SAE and which may need to be considered by the individual reviewing the event.

Q12. Record details of study drug(s). This section must be completed regardless of whether there is a causal relationship with the study drug(s).

Page 3

Q13. Use the table to list all concomitant medications and use additional pages (P3a section 13a) if required.

ARCHIE ID: ☐☐☐/☐☐☐☐

Serious Adverse Event Report Form

13. Concomitant medication *(generic names only):* None ☐ **OR**

Describe all non-study medication taken at the time of onset of the event and medication given to treat the SAE including prescription, non-prescription and over-the-counter medication.

Medication	Indication	Given to treat SAE	Dose	Frequency	Route	Date started	If discontinued, date stopped
		☐				D D / M M / Y Y	D D / M M / Y Y
		☐				D D / M M / Y Y	D D / M M / Y Y
		☐				D D / M M / Y Y	D D / M M / Y Y
		☐				D D / M M / Y Y	D D / M M / Y Y
		☐				D D / M M / Y Y	D D / M M / Y Y
		☐				D D / M M / Y Y	D D / M M / Y Y
		☐				D D / M M / Y Y	D D / M M / Y Y
		☐				D D / M M / Y Y	D D / M M / Y Y

Did you document further concomitant medications on the supplementary SAE report page 3a? Yes ☐ No ☐

If Yes, how many pages did you complete? ☐

Internal Use Only
SAE Identifier: ____________________

ARCHIE ID: ☐☐☐/☐☐☐☐

Serious Adverse Event Report Form

13a. Concomitant medication *(generic names only):*

Describe all non-study medication taken at the time of onset of the event and medication given to treat the SAE including prescription, non-prescription and over-the-counter medication.

Medication	Indication	Given to treat SAE	Dose	Frequency	Route	Date started	If discontinued, date stopped
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY
		☐				DD/MM/YY	DD/MM/YY

Internal Use Only
SAE Identifier: _____

ARCHIE ID: ☐☐☐/☐☐☐☐

Serious Adverse Event Report Form

Form completion instructions overleaf

14. Outcome of event: *(tick one box only)*

Resolved ☐ Resolving ☐ Not resolved ☐

Resolved with sequelae ☐ Unknown ☐ Fatal ☐

If fatal, give date of death: D D / M M / Y Y

Was a post-mortem performed/ is one planned? Yes ☐ No ☐

If Yes, give date of post-mortem: D D / M M / Y Y

15. Is there any further information to come? Yes ☐ No ☐

NB: Follow-up information should be submitted on any unresolved event until resolution (please use another SAE Report Form, and only report any new or changed information).

16. Reporter's signature: _____

Date: D D / M M / Y Y

Print name: _____

Position: _____

Telephone number: ☐☐☐☐☐☐☐☐☐☐☐

Further contact details *(e.g. bleep/pager number, please specify)*:

_____

IMPORTANT: This section of the SAE report is to be completed by a medically qualified individual only.

17. Causality of the Serious Adverse Event:

The Reporting Clinician's decision on relationship to the IMP *(tick one box only)*

Not related ☐ Possibly ☐ Probably ☐ Definitely ☐

I confirm that I have reviewed Pages 1, 2, 3 and 4 of the Serious Adverse Event report and that all data are correct.

Assessor's signature: _____ **Date** D D / M M / Y Y

Print name: _____ **Position:** _____

Telephone number ☐☐☐☐☐☐☐☐☐☐☐

Further contact details *(e.g. bleep/pager number, please specify)*:

_____

If this information is not available at the time the SAE is first reported, please re-send all pages of this report once completed.

Q14. Select **one** of the outcome options. If the outcome is “Resolving” or “Not Resolved” then complete a follow-up report when the status of the SAE changes.

Q16. Include a telephone number for the person reporting the SAE so that the individual assessing the event can contact them in case of queries or if clarifications are needed.

Q17. A medically qualified individual is responsible for reviewing the SAE and considering whether the event was related to the study drug(s).

If a medically qualified individual is not available to make the causality assessment send in the SAE Reporting Form without this information and re-send the form as soon as this assessment has been made.

14.4 See Section 10.3 Working Instruction WI 06

Formerly called Trial Specific Procedure TSP 06 - Serious Adverse Event Reporting

14.5 Copies of completed SAE/SUSAR forms

14.6 SAE/SUSAR related correspondence