**THE CREAM STUDY – CHILDREN WITH ECZEMA, ANTIBIOTIC MANAGEMENT STUDY.**

Version 2.1 27/11/2013

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| **Sponsor:** | Cardiff University, 7th Floor, 30-36 Newport Road, Cardiff, CF24 ODE |
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**This protocol has been authorised by:**

| | | | |
|---|---|---|---|
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| **Name** | **Role** | **Signature** | **Date** |
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| | | | **27/11/2013** |
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## I. Statement of compliance

**General Information** This protocol describes the CREAM clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but centres entering patients for the first time are advised to contact the South East Wales Trials Unit (SEWTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred, in the first instance, to the South East Wales Trials Unit.

**Compliance** This trial will adhere to the conditions and principles which apply to all clinical trials as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, EU Directive 2001/20/EC, EU Directive 2005/28/EC and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), as amended, the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2001 and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

**Funding** The CREAM trial is being funded by the National Institute for Health Research Heath Technology Assessment Programme (NIHR HTA).

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**Please contact the Trial Manager for general queries and supply of trial documentation**

## Randomisations:

**Randomisation**

Randomisation of trial participants will be achieved through the use of unique pre-labelled study medication packs. **Please contact the Trial Manager at South East Wales Trials Unit on 07891830421 if unblinding is required.**

## Clinical Queries:

**Clinical Queries**

**All clinical queries should be directed to the Trial Manager (Tel: 029 2068 7665) who will direct the query to the most appropriate clinical person.**

## Serious Adverse Events:

**SAE reporting**

**Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and faxed to the CREAM Trial Manager within 24 hours upon becoming aware of the event. (See Section 12 for more details).**

**Fax Number: 02920 687 612**

## III. Table of contents

## IV. Glossary of abbreviations

| | |
|---|---|
| **AE** | Adverse Event |
| **AD** | Atopic Eczema/Atopic Dermatitis |
| **AR** | Adverse Reaction |
| **BNF** | British National Formulary |
| **CACE** | Complier Average Causal Effect |
| **CAE** | Cost Effectiveness Analysis |
| **CDLQI** | Children's Dermatology Life Quality Index |
| **CI** | Chief Investigator |
| **CRF** | Case Report Form |
| **CTA** | Clinical Trials Authorisation |
| **CUA** | Cost Utility Analysis |
| **DFI** | Dermatitis Family Impact |
| **EASI** | Eczema Area and Severity Index |
| **EHR** | Electronic Health Record |
| **EudraCT** | European Clinical Trials Database |
| **ICH** | International Conference on Harmonization |
| **IDQol** | Infants Dermatology Quality of Life instrument |
| **GCP** | Good Clinical Practice |
| **GP** | General Practitioner |
| **GMP** | Good Manufacturing Practice |
| **HTA** | Health Technology Assessment |
| **HRQoL** | Health-Related Quality of Life |
| **IB** | Investigator Brochure |
| **IDMC** | Independent Data Monitoring Committee |
| **IMP** | Investigational Medicinal Product |
| **IRAS** | Integrated Research Application System |
| **ISRCTN** | International Standard Randomised Controlled Trial Number |
| **MHRA** | Medicine and Healthcare products Regulatory Agency |
| **NHS** | National Health Service |
| **NICE** | National Institute for Clinical Excellence |
| **NIHR** | National Institute for Health Research |
| **PI** | Principal Investigator |
| **PID** | Participant Identification Number |
| **PIL** | Patient Information Leaflet (pack insert). |
| **PIS** | Participant Information Sheet |
| **POEM** | Patient-Orientated Eczema Measure |
| **QALY** | Quality-adjusted Life Years |

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|---|---|
| **QL (QoL)** | Quality of Life |
| **QP** | Qualified Person |
| **R&D** | Research and Development |
| **REC** | Research Ethics Committee |
| **RCT** | Randomized Controlled Trial |
| **SAE** | Serious Adverse Event |
| **SACU** | Specialist Antimicrobial Chemotherapy Unit |
| **SAR** | Serious Adverse Reaction |
| **SARMA** | Scottish Acute Recruitment Multi-Agent |
| **SATT** | Stand-Alone Trial Torrent |
| **SEWTU** | South East Wales Trials Unit |
| **SOP** | Standard Operating Procedure |
| **SmPC** | Summary Product Characteristics |
| **SUSAR** | Suspected Unexpected Serious Adverse Reactions |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |
| **UK CRC** | United Kingdom Clinical Research Collaboration |
| **WTE** | Whole Time Equivalent |

# 1 Amendment History

| Amendment No. | Protocol version no. | Date issued | Author(s) of changes | Details of changes made |
|---|---|---|---|---|
| 1 | 1.1 | 19/06/12 | I Haq | Update of Exclusion Criteria to reflect "Used oral or topical antibiotics within the past week." |
| 2 | 1.2 | 16/08/12 | I Haq | • Updated SAE reporting and included 24 unblinding. |
| 3 | 1.3 | 31/08/12 | N Kalebic | • Updated SAE reporting (p.5) and serious AS/Aes (p.40) from "within one working day" to "within 24 hours". |
| 4 | 1.4 | 12/02/13 | I Haq | • Updated the 24 hour blinding contact number to the new mobile number 07891830421. |
| 5 | 1.5 | 11/06/13 | I Haq | • Update to archiving of data changed from minimum 15yrs to until youngest participant is 21. In accordance to Sponsor SOP. |
| 6 | 1.6 | 29/07/13 | I Haq | • Update minimisation criteria for Trial Torrent (p.26)<br>• Update with new +/- threshold for various data collection timepoints (p.45) |
| 7 | 2.0 | 05/11/13 | I Haq | • Update all aspects of the protocol to clarify changes to data collection:<br>o photographs will no longer be taken at the baseline visit.<br>o The week 1 visit will be stopped. Study Trial Packs (medication) will be collected at week 2 visit.<br>• Inclusion and exclusion criteria updated. |
| 8 | 2.1 | 27/12/2013 | I Haq | • Correct changes to staff training to ensure all research nurses and teams are trained on study procedures. |

# 2 Synopsis

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|---|---|
| **Study Acronym** | CREAM |
| **Study Title** | The CREAM Study – Children with Eczema, Antibiotic Management Study |
| **Clinical Phase** | Phase IV |
| **Trial Design** | Double blinded, 3-arm randomised controlled trial |
| **Trial Participants** | Children aged 3 months to less than 8 years with suspected infected atopic eczema. |
| **Planned Sample Size** | A total of 411 participants need to be followed up. Allowing for 20% loss to follow-up we will aim to recruit 516 participants (172 per centre). |
| **Follow-up duration** | 12 months in total (assessment at baseline, 2 weeks, 4 weeks, 3 months and 12 months). |
| **Planned Trial Period** | 36 months |
| **Primary Objective** | To provide a rigorous answer to the question:<br>Does the addition of oral or topical antibiotic treatment to treatment with corticosteroid cream, reduce eczema severity in children with infected eczema in primary care? |
| **Secondary Objectives** | 1. Assess the short-term effectiveness of oral and topical antibiotics in terms of effect on subjective and objective severity, quality of life, impact on family, and daily symptoms.<br>2. Assess the effectiveness of oral and topical antibiotics on subjective and objective severity, and quality of life at 3 months.<br>3. Compare oral and topical antibiotic treatments in terms of short and long-term effects, adverse effects, parent preference, and effect on prevalence of colonisation/infection with resistant organisms.<br>4. Assess the short and long-term cost-effectiveness of treating suspected atopic eczema with oral or topical antibiotics, in terms of cost per unit reduction in subjective outcome severity.<br>5. Undertake an exploratory cost utility analysis using a new condition-specific preference-based measure of health for |

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| | children.<br>6. Describe the prevalence of *Staphylococcus aureus* isolates, and patterns of resistance, in patients with suspected infected eczema, and describe the long-term prevalence of resistant isolates in those using oral antibiotics, topical antibiotics, and placebo. |
| **Primary Endpoint** | Assessment of subjective severity of eczema at two weeks (as measured using the validated Patient-Orientated Eczema Measure (POEM)) |
| **Secondary Endpoints** | • Objective eczema severity (Eczema Area and Severity Index (EASI))<br>• Quality of life (Infants Dermatology Quality of Life instrument (IDQol)) or Children's Dermatology Life Quality Index (CDLQI).<br>• Impact on Family (Dermatitis Family Impact (DFI instrument)) |
| **Investigational Medicinal Products** | Oral antibiotic suspension - flucloxacillin <u>or</u> erythromycin if penicillin allergic<br>Matching oral placebos<br>Topical antibiotic - fusidic acid 2% cream<br>Matching topical placebo |
| **Form, Route, Dose and Regime** | **<u>Group 1: Oral Antibiotic and Topical Placebo</u>**<br>• Oral antibiotic<br>o Flucloxacillin 250mg per 5mL.<br>▪ For children aged 3 months to 2 years - 2.5mL four times a day for 7 days.<br>▪ For children aged over 2 years to under 8 years - 5mL four times a day for 7 days.<br>o <u>Or</u> erythromycin 250mg per 5mL if penicillin allergic.<br>▪ For children aged 3 months to 2 years - 2.5mL four times a day for 7 days.<br>▪ For children aged over 2 years to under 8 years - 5mL four times a day for 7 days.<br>• Topical placebo<br>o Apply cream to affected area(s) three times a |

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| | day for 7 days.<br><br>**<u>Group 2: Oral Placebo and Topical Antibiotic</u>**<br>• Oral placebo<br>  o For children aged 3 months to 2 years - 2.5mL four times a day for 7 days.<br>  o For children aged over 2 years to under 8 years - 5mL four times a day for 7 days.<br>• Topical antibiotic - fusidic acid 2% cream.<br>  o Apply cream to affected area(s) three times a day for 7 days.<br><br>**<u>Group 3: Oral Placebo and Topical Placebo</u>**<br>• Oral placebo<br>  o For children aged 3 months to 2 years give 2.5mL four times a day for 7 days.<br>  o For children aged over 2 years to under 8 years give 5mL four times a day for 7 days.<br>• Topical placebo<br>  o Apply cream to affected area(s) three times a day for 7 days.<br><br>All treatments will be given for one week, following which treatment will revert to usual care.<br><br>**<u>Groups 1, 2 and 3</u>:**<br>All patients will receive topical clobetasone butyrate 0.05% (Eumovate) cream or ointment (for eczema on trunk and/or limbs) and/or topical hydrocortisone 1% cream or ointment (for eczema on face).<br>All patient carers will also receive advice about standard eczema care. |

# 3 Trial summary & schema

## 3.1 Trial summary

CREAM is a 3-arm, double-blind, randomised controlled trial to determine the clinical and cost effectiveness of the most commonly used oral and topical antibiotics, in addition to topical corticosteroids, in the management of suspected infected atopic eczema in children. CREAM will be based in primary and secondary care settings. Participating clinicians will identify children (aged under 8) with eczema and features suggestive of infection. Children with severe infections or conditions making them more vulnerable to infection will be excluded from the study. Following informed consent from the parent/carer(s), children will be randomly assigned to one of three treatment groups (all for one week): 1. Oral antibiotic and placebo cream, 2. oral placebo and antibiotic cream, or 3. oral placebo and placebo cream. All participants will receive standard advice about eczema care and corticosteroid cream(s) (moderate potency for trunk and limbs, mild for face).

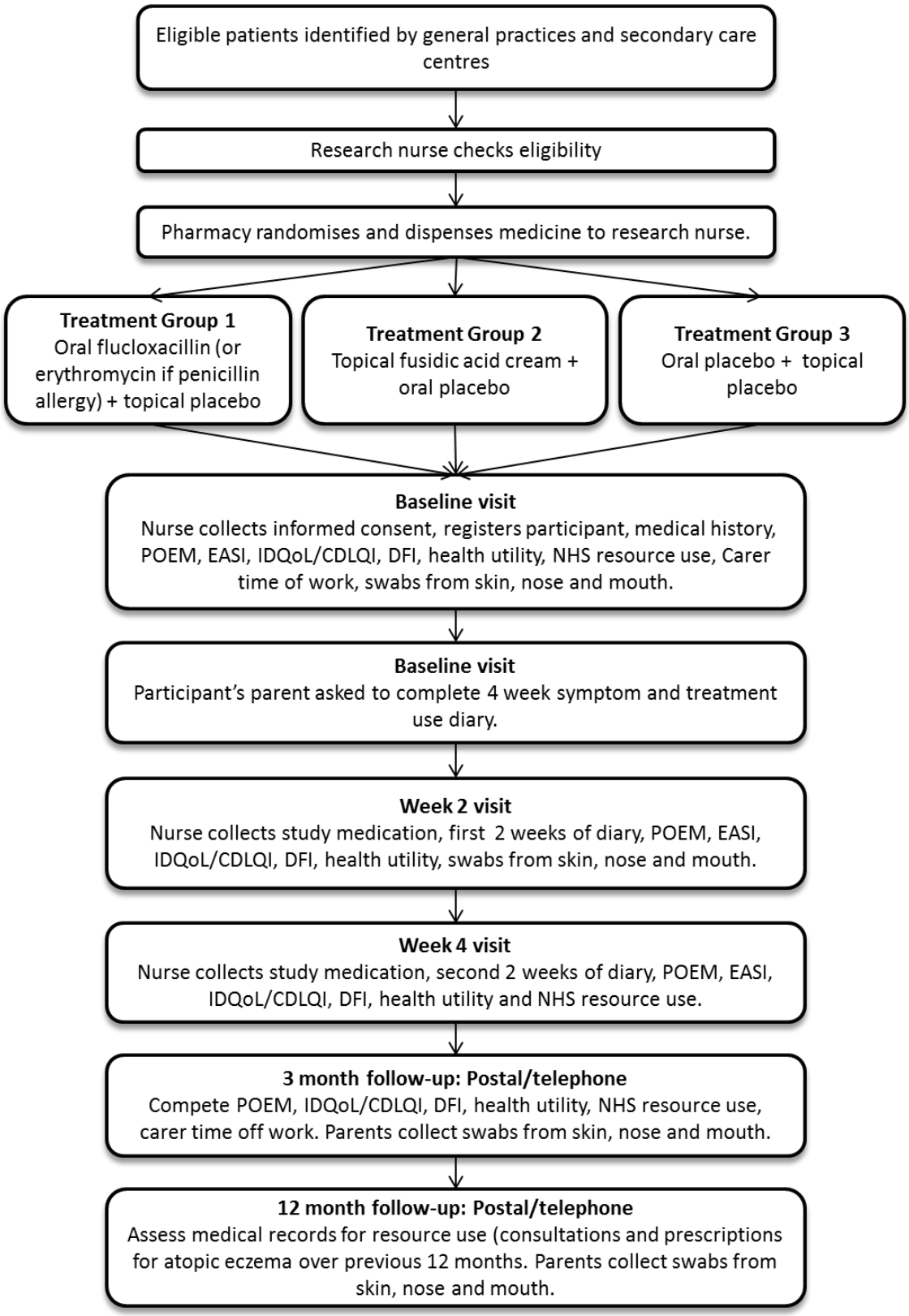
At the baseline visit, a trained research nurse will assess the extent and severity of eczema, quality of life, and impact of the eczema on the family, and health status, using established assessment tools. At the 2 week visit the research nurse will collect unused medication. At 2 and 4 weeks, the research nurse will visit to assess severity, quality of life, and impact on the family, as well as asking about side effects and costs (so that we can conduct an economic evaluation). The parent/carer(s) will be asked to complete a diary for the first 4 weeks to record symptom severity, use of medication, and healthcare consultations. Participants will also be followed-up by a postal or telephone questionnaire at 3 months (participants who do not return the postal questionnaire will be telephoned to see if they would prefer to complete a telephone-administered questionnaire), to assess eczema severity, quality of life, impact on the family, and costs. At 12 months we will conduct a search of participants' primary care medical records in order to identify healthcare consultations, drugs prescribed, subsequent episode of infected eczema and use of antibiotics for the infected eczema. We will take skin, mouth and nose swabs at the baseline and the 2 week visit, and ask the parent/carer(s) to take these swabs at 3 and 12 months, to assess impact of treatments on bacterial resistance. Asking parents to take swabs has been shown to be effective and acceptable to parent/carer(s) and children. Training on how to take these swabs will be provided to parents by the research nurses during the 2 and 4 week follow-up visits.

The main analysis will compare subjective eczema severity during the second study week (i.e. the week following completion of treatment), using established questionnaires completed by the child's parent/carer(s), in those in each of the two active treatment groups (oral and topical antibiotics) with the placebo group.

## 3.2 Trial schema and participant flow

The schedule of events and participant flow for the trial is summarised in Figure 1. Full details of assessments performed (clinical and non-clinical) are presented in Section 13.

**Figure 1: Trial Schema and participant flow diagram**



# 4 Introduction

## 4.1 Background

### 4.1.1 Eczema

Atopic eczema (also known as atopic dermatitis (AD)) is one of the most common childhood disorders [1] [2]. Of those affected, 45% develop symptoms within the first six months of life and 85% by the age of five years [3]. The lifetime prevalence by age 6-7 years is approximately 35% [4] [5], and is continuing to rise [6].

A cross-sectional survey of 1-5 year olds in four general practices in the Nottingham area identified 290 children with AD (confirmed by a dermatologist) during a one-year period (16% period prevalence). Of these, 96% consulted in primary care and 6% consulted in secondary care about their eczema during the year. Using census data, the authors estimated the annual UK cost of AD in children 1-5 years in 1995-96 as £47 million [7].

### 4.1.2 Effect on quality of life

AD can have a significant impact on the quality of children's life and that of their family - the more severe the eczema the greater the effect [8]. For the child, AD can adversely influence their emotional and social development[9] and may predispose to psychological difficulties [10]. Parents report loss of sleep and stress, and families can become socially isolated [3].

A study of 379 children aged 5-16 years with skin disease of more than 6 months duration found that AD (and Psoriasis) resulted in the greater impairment of quality of life than other skin conditions, including urticaria and acne. Furthermore, generalised AD was rated as causing greater impairment in quality of life than renal disease, cystic fibrosis, asthma, epilepsy, and diabetes [11]. The predominant symptom of itching causes sleep disturbance in over 60% of children [12]. In addition, there are significant burdens for the families of children suffering with AD. For example, parents report having to take time off work and financial loss as a result of caring for their child [7].

### 4.1.3 Staphylococcus aureus and atopic eczema

AD is a relapsing and remitting condition, yet there is considerable uncertainty about the cause of flares [13] [14]. *Staphylococcus aureus* (*S. aureus)* has long been known to be associated with AD. The organism can be isolated from around 90% of patients with AD [15] [16] compared with between 5% and 25% of healthy subjects

[15 17]. Furthermore, more severe eczema is associated with higher densities of the organisms [15 17 18].

There is evidence that a number of factors contribute to this propensity for colonisation and infection, including: dysregulation of the adaptive immune response, reduced antimicrobial peptide levels, diminished recruitment of cells to the skin, Toll-like receptor defects, and epidermal barrier abnormalities [19]. The exact role of *S. aureus* in the maintenance or exacerbation of AD is not clear. However, there is increasing evidence for the role of toxins with superantigenic properties (superantigens) [19].

### 4.1.4 Use of antimicrobial treatments for atopic eczema

Despite the clear evidence for a relationship between AD and *S. aureus*, the evidence for benefit from eliminating the organism is far less clear. A recent Cochrane systematic review, which included 21 studies and 1018 participants, failed to find convincing evidence of benefit from antimicrobial interventions for people with clinically uninfected and clinically infected AD. The authors concluded that, "Further large studies with long-term outcomes and clearly defined participants are urgently required" [20].

This is important not only because of the need to identify effective treatments for children with AD. Widespread use of antimicrobials where there is unclear evidence of benefit contributes to the development of antimicrobial resistance and exposes children to possible harms from adverse effects.

## 4.2 Rationale for current trial

This study will lead to benefits for patients and the public by filling the evidence gap regarding treatment of an important and common condition (atopic eczema). Oral and topical antibiotics are widely used to treat eczema in primary care and yet there is insufficient evidence to be sure whether this 'hand-me-down' practice either helps or harms patients, and if antibiotics help, which route (topical or oral) does most good and causes least harm. Furthermore, widespread use of antibiotics drives bacterial resistance, which pose an important public health threat.

# 5 Trial objectives

## 5.1 Primary objective

- To assess the effectiveness of oral and topical antibiotics on subjective eczema severity during the week following treatment.

## 5.2 Secondary objectives

- Assess the short-term (up to four weeks) effectiveness of oral and topical antibiotics on subjective and objective severity, quality of life, impact on family, and daily symptoms.
- Assess the effectiveness of oral and topical antibiotics on subjective and objective severity, and quality of life at 3 months.
- Compare oral and topical antibiotic treatments in terms of short and long-term effects, adverse effects, parent preference, and effect on prevalence of colonisation/infection with resistant organisms.
- Assess the short and long-term cost-effectiveness of treating suspected atopic eczema with oral or topical antibiotics, in terms of cost per unit reduction in subjective outcome severity.
- Undertake an exploratory cost utility analysis using a new condition-specific preference-based measure of health for children.
- Describe the prevalence of *Staphylococcus aureus* isolates, and patterns of resistance, in patients with suspected infected eczema, and describe the long-term prevalence of resistant isolates in those using oral antibiotics, topical antibiotics, and placebo.

# 6 Trial Design

The CREAM trial will be led by Co-Chief Investigators (CI) (Dr Nick Francis, Cardiff and Prof Frank Sullivan, Dundee). The study will be coordinated by the South East Wales Trials Unit (SEWTU), and conducted in regional centres in Wales, Scotland, and England. Each region will be led by a regional principal investigator.

The study comprises a three-arm, double-blind, randomised placebo controlled trial involving children with suspected infected eczema. A total of 516 participants will be randomised to receive either; i) oral antibiotic suspension plus topical placebo cream, ii) topical antibiotic cream plus oral placebo suspension or, iii) oral placebo suspension plus topical placebo cream.

# 7 Centre and investigator selection

## 7.1 Trial Site and Investigator Team

The study will be performed at the participant's home or suitable location, as determined by discussion between the research nurse and participant's parent/carer(s). General practices and dermatology clinics will act as sites to refer eligible patients to the research nurse in their region. General Practices and dermatology clinics (will be considered as sites for the purpose of the trial, and will be under the responsibility of the Principal Investigator (PI) for their region. All sites, research nurses, site pharmacies and research centres will be provided training on study procedures and protocols. Consent, registration and assessments of patients will be the responsibility of the research nurse and coordinated by their regional research site and the Trial Manager. The overall responsibility for the study will rest with the Co-chief Investigators, Dr Nick Francis and Prof Frank Sullivan. The Trial Manager will act on behalf of the Co-chief Investigators to ensure the smooth and efficient running of all aspects of the study.

Co-investigators will provide clinical and scientific expertise for the trial, together with the trial management team. The PI will delegate study related activities to appropriate trained and qualified personnel according to staff responsibilities and job descriptions. This will be documented in a study specific Delegation of Responsibilities form.

Each centre will take responsibility for regional recruitment and trial management within their region. SEWTU will lead the overall data management including design of data collection and entry tools, monitoring data quality, liaison with the research laboratory and coordinating each centre's research team. The principle investigators will liaise with their local National Health Service (NHS) Trust Pharmacy to ensure a suitable agreement between the Sponsor and the Pharmacy in each region. The pharmacy in each site will become the local Site Pharmacy and be responsible for randomisation and dispensing the trial medication as explained in section 11.4.

### 7.1.1 Recruitment of sites

General practices and dermatology units will act as sites. The procedure for recruiting general practices and secondary care centres may vary between the regional centres. Potential sites will either be contacted directly by the local study team or through a local research network. Practices or dermatology units that

express an interest in the study will be sent written information about the study, which will be followed up by telephone conversations and/or a visit.

Practices and/or dermatology units agreeing to participate will be sent a 'Training Pack', which will contain documentation required to become a CREAM Study site, including a study agreement and the documents required for referring patients and prescribing treatments.

It is the responsibility of each PI to ensure the following documents are received by the CREAM Trial Manager (see contact details at front of protocol):

- A signed Site Agreement.
- Completed Signature List and Roles and Responsibilities document.
- Completed contacts list of all practice personnel working on the Study.
- A completed and signed Site Specific Information Sheet (where required)

Upon receipt of all the above documents, the CREAM Trial manager (or delegate) will send a confirmation letter to the Principal Investigator of the region, the research nurse, and the clinician(s) at the site, confirming that their practice/centre now ready to start identifying potentially eligible patients. This letter must be filed in their Site File.

# 8 Participant selection

Children are eligible to join the trial if they meet the following inclusion criteria (section 8.1) and do not meet any of the exclusion criteria (section 8.2). All queries about patient eligibility should be directed to the CREAM Trial Manager before randomisation (administration of study medication).

## 8.1 Inclusion criteria

Children (aged 3 months to less than eight years) with atopic eczema (as defined by UK working party (Appendix I)) who are presenting with **a clinical suspicion of infected eczema**. This could include children where:

- The eczema is failing to respond to standard treatment with emollients and / or mild - moderate topical corticosteroids.
- There is a flare in the severity or extent of the eczema.
- There is weeping or crusting.

## 8.2 Exclusion criteria

Children will not be eligible for inclusion if they **have**:

- Used oral or topical antibiotics to treat a skin infection within the past week.
- Have used potent or very potent topical corticosteroids (Appendix IV) within the past two days.
- Treating clinician believes the patient has a severe infection requiring immediate antibiotics or is arranging immediate hospitalisation or urgent (same or next day) dermatology referral because of the severity of the eczema or suspected infection.
- Features suggestive of eczema herpeticum (significant pain, punched out lesions).
- Known significant comorbid illness (e.g. significant immune compromise)
- Allergy to fusidic acid or both penicillin and erythromycin.
- Contraindication to any study medication (penicillin, erythromycin, fusidic acid).

Or if they **do not have**:

- A parent or legal guardian who is able to provide written informed consent.
- A parent/legal guardian (or a person delegated by the parent/legal guardian) who expects to be available for follow-up visits at 2, and 4 weeks and who understands English well enough to complete simple verbal and written questionnaires.

# 9 Recruitment of participants

## 9.1 Number of participants

A total of 516 participants will be required.

## 9.2 Recruitment procedure

Participating clinicians will be asked to sequentially identify suitable children during routine consultations. Some clinicians will be aided in the identification of suitable children through the use of a software package – Trial Torrent software (see 9.2.5.1 below).

### 9.2.1 Informing parents of potentially eligible children about the trial

Following set up of general practice sites and dermatology units, we will ask the site to identify all children less than 8 years of age who have a history of eczema recorded in their electronic medical record and to write to their parent/legal guardian(s) (herein referred to as parent/carer(s)) to inform them about the

study. The purpose of this letter is to provide parent/carer(s) with advanced notification and information about the study; including the potential risks and benefits of taking part, in order to facilitate their decision about participation should their child develop a possible infection during the course of the study.

### 9.2.2 Identification of potentially eligible children

Potentially eligible children will be identified by clinicians at the time of consulting. The clinician will explain the study to the child's parent/carer(s), and provide them with a written participant information sheet (PIS).

### 9.2.3 Parent/carer(s) is interested in their child taking part

The clinician will ask interested parent/carer(s) for verbal consent to pass to the research team, i) contact details and ii) details of the child's current illness and penicillin allergy status.

Clinicians will record examination findings, working diagnosis, current treatment and penicillin allergy status on a paper log or electronic case report form (CRF) depending on whether the practice is using the Trial Torrent software or not (see section 9.2.5 below). This data will be used to help assess eligibility and need for non-penicillin treatment.

The clinician will also prescribe corticosteroid cream(s) or ointment(s) for all children (Eumovate for trunk and limbs and/or 1% hydrocortisone for face), emollients if the parents do not already have a supply sufficient for at least two weeks (the choice of emollient to be decided by the clinician in conjunction with the parent/carer(s), however emollients containing antimicrobial agents must not be used) and give advice on optimal care of eczema (including an information leaflet).

Finally, the clinician will complete a study prescription for study medication on a triplicate form. One copy of this form will be kept by the general practice, and will be used to fax a copy to the study pharmacy. The clinician will provide the parent/carer(s) with a trial information folder containing the original and a copy of the prescription. When the research nurse meets the parent/carer(s) at the baseline appointment, the research nurse will collect the original and copy of the prescription from the parent/carer(s). The research nurse will keep the copy, and deliver the original prescription to the study pharmacy.

### 9.2.4 Parent/carer(s) is not interested in their child taking part

If the parent/carer(s) is not interested in participating at this point the study team will not contact them. Clinicians will be asked to keep a log of non-

identifiable information, including the reasons for non-consent (where given by the parent/carer(s)), for all eligible children who are not recruited into the study. These data will be used to assess for selection bias. The clinician will continue to treat the child according to their usual practice.

### 9.2.5 Use and evaluation of the recruitment software

#### *9.2.5.1 Trial Torrent software*

We plan on using the Trial Torrent software package (formerly known as Scottish Acute Recruitment Multi-Agent (SARMA)) [21] to aid in the identification of suitable patients and notification of the research team that a suitable participant is interested. All practices will be encouraged to have this package installed on their practice computers, but use of the software will not be a requirement of participation. In order to evaluate its effectiveness as a tool to aid recruitment (see Section 9.2.5.2), Trial Torrent will only be activated as a prompt for clinicians in some practices. For the evaluation, practices will be randomised based on a randomisation schedule.

Trial Torrent sits on the practice's computers and links with their clinical software system in order to identify when pre-programmed Read codes (codes used in general practice computer systems to identify symptoms, diagnoses, or medications) are used by the clinician. In practices randomised to use of the recruitment software a pop-up box will notify the clinician that the patient may be eligible for inclusion. This box can be used to indicate whether the patient has been given additional information, and if so, whether the patient's parent/legal guardian has verbally consented to have their information transmitted to the research team. In addition, for those who agree to a visit from the research nurse, the software can be used to record additional information (such as clinical features) and send these along with patient contact details and penicillin allergy status directly to the research team using a secure website, email and/or SMS messaging.

This software has been developed in conjunction with the major manufacturers of general practice clinical software systems in the UK, and has been previously used in a UK primary care study. The system integrates with the practice electronic health record (EHR) system using an approach that is carefully designed to minimise load on the host system. Consequently, there should be no noticeable effect on performance. The system is also secure and will only transmit data that patients (or their parent/carer) have consented to pass on.

In the remaining practices, although pop-up prompts will not appear, clinicians will have the option of using the Trial Torrent software to pass clinical and contact

details to the nurse. Furthermore, clinicians who do not have Trial Torrent installed and those randomised to not have Trial Torrent prompts, can choose to send patient details via a web portal (Stand-Alone Trial Torrent (SATT)) or by fax.

Clinicians who fax will be asked to fax a referral form to a secure fax machine in the research centre to indicate that a potential participant has been identified. The research centre will contact the research nurse via SATT.

If at the baseline visit a patient's parent/carer(s) does not fully consent to participating in the study, data held in relation to the referral, on electronic devices, such as mobile phones and Trial Torrent servers will be deleted and/or anonymised as required by a CREAM-specific standard operating protocol.

#### *9.2.5.2 Evaluation of the Trial Torrent software*

We have been asked by our research funders to evaluate use of this recruitment aid. In order to do this we will conduct a nested evaluation. GP Practices that are willing to use Trial Torrent will be randomly assigned to receive Trial Torrent prompts or not. Randomisation will occur at the time of practice enrolment and will be minimised by list size (less than 6,000, greater than 6,000) and whether the practice is research active or not in the past 12 months.

At three and six months (from the start of patient recruitment) we will compare the **mean recruitment rate** (recruited patients per month recruiting per whole time equivalent (WTE) participating clinician) for GP practices in each arm (of the Trial Torrent evaluation). In addition, at three months from the start of recruitment the Trial Statistician will compare the **time to first patient recruited** in the two groups and present analysis to the TMG. If we find a significant improvement in either the mean recruitment rate or time to first patient recruited at three months or in mean recruitment rate at six months then the evaluation will be stopped and the Trial Torrent software will be rolled-out to the rest of the practices. If no significant improvement is found at either of these time points then we will continue the evaluation until the end of the recruitment period (12 months) and compare the mean recruitment rate in the two arms at this time. Since the analysis of the mean recruitment rate at 3 and 6 months are interim analyses the significance level for those tests needs to be adjusted if we are to retain an overall significance level of 5%. The Pocock method will be used implying a significance level of 0.022 will be used for all three analyses [22]. This will facilitate the early stopping of the sub-study if it is found to improve recruitment. With 90 practices we would have a power of 84% for detecting a

hazard ratio of 0.5 with an estimated standard deviation of 0.5 and at the 2.2% significance level.

## 9.3 Informed Consent

The research nurse will contact parent/carer(s) (within 48 hours) who have agreed to have their contact details passed to the research team, and arrange to visit them at their home or another mutually acceptable location within 72 hours (usually 48 hours) of their clinic consultation. During the visit the nurse will discuss study participation in detail, check eligibility, answer questions and check understanding, and ask parents to provide informed consent for their child's participation. The parent/carer(s) will be given as much time as they require for reading the study materials and for asking questions.

Consent will be taken by a research nurse who will have been trained in taking informed written consent. At least one parent or legal guardian must provide informed consent in order for the child to be enrolled in the study.

We will comply with Welsh language requirements and the PIS, Consent Form and any other required participant documentation will be available in Welsh. However, all documentation used for data collection (i.e. outcome measures) will remain in English as they are designed and validated in English.

## 9.4 Randomisation, blinding and unblinding

Randomisations lists will be prepared by the study statistician. Each Site Pharmacy will be provided with two randomisation lists, one for patients not allergic to penicillin and one for those who are. These will be block randomised with randomly chosen balanced blocks of six or nine. As patients are recruited they are assigned the next vacant Participant Identification number (PID). The randomisation list will link each unique PID to a treatment group, denoted A, C or E for the non-penicillin allergic group; and B, D and F for the penicillin allergic group. The pharmacist will then select a treatment pack(s) for the relevant treatment arm based on a trial pack randomisation list. This is to ensure that trial pack identification numbers cannot be used to identify treatment allocation. The Trial Pack contains the prescribed medication as detailed in Section 11.3. The process is described in more detail in the Trial Pack Randomisation Protocol.

At the point when a research nurse arranges to visit a potential participant, they will inform their local Site Pharmacy who will begin preparing a Trial Pack based on the faxed prescription received from the clinician and the randomisation list.

Therefore, site pharmacists will not be blinded, but the research nurses will remain blinded at all times.

The research nurse will collect the Trial Pack(s) from the Site Pharmacy and transport the Trial Pack to the patient's home. The research nurse will only release Trial Pack(s) once informed consent has been obtained and a Consent Form signed. Participant randomisation will be considered to have occurred once a Consent Form has been signed and the Trial Pack opened. The Trial Pack number will then have been entered onto the participant's CRF. If consent is not obtained then the Trial Pack will be returned to the study pharmacy, logged and destroyed. Further details for IMP destruction will be provided to the research nurse and site pharmacies in a trial-specific IMP management standard operating protocol.

### 9.4.1 Blinding

Clinicians at sites and research nurses will remain blinded throughout the study, unless they are providing clinical treatment to a serious adverse event, in which case they can contact the research centre for unblinding.

Site pharmacists will not be blinded as they are required to randomise, prepare and dispense the correct Trial Pack(s).

### 9.4.2 Unblinding

The treatments used in this study are all licensed products (or their placebos) used within their licensed indications, and the participants will be provided with information about the medication they may be on (i.e. Flucloxacillin, or its placebo; erythromycin, or its placebo; fusidic acid, or its placebo). The most likely adverse event that may necessitate unblinding is a possible allergic reaction to study medication. Furthermore, if a serious adverse event (SAE) (Section 12) occurs or unblinding is required for any reason, we will provide a 24 hours a day unblinding service.

Research nurses will advise parent/carer(s) to contact NHS Direct, their primary care out-of-hours provider, or the emergency ambulance service if the participant should require out-of-hours medical attention. The parent/carer(s) will be advised to ensure they provide the participant's Trial Pack, Patient Information Leaflet (PIL) and other trial documentations to the treating clinician(s). This information will notify the treating clinician(s) that the participant is either taking flucloxacillin suspension or erythromycin suspension orally, or their placebos, or applying fusidic cream or its placebo.

All Trial Packs will contain a PIL for each study medication, and all participants provided a PIS by the research nurse which will include information on unblinding. In the event that a clinician treating a study participant feels the need to know the study medication that a participant is taking (or has taken), they can request unblinding of that participant's study medication by telephoning the number below 24 hours a day. Randomisation lists will be kept in a secure location that is accessible to staff providing the unblinding service.

**Contact SEWTU for unblinding:**
**Tel: 07891830421**

### 9.5 Screening logs

Trial Torrent software will record the number of children with Read Codes suggesting a consultation for infected eczema each month, and these data will be used to assess for possible selection bias.

## 10 Withdrawal & loss to follow-up

Parent/carer(s) will be informed that they have the right to withdraw consent for their child's participation in any aspect of CREAM Trial at any time. If a parent/carer indicates that they wish to withdraw their child from the trial they will be asked to give, though are not required to provide, a reason for withdrawal. The participants' care will not be affected by declining to participate or withdrawing from the trial.

If participants initially consent but subsequently withdraw from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

- Withdrawing from trial treatment but happy to be followed up.
- Withdrawing from nurse follow-up (swabs and/or objective measures).
- Withdrawing from questionnaire/telephone follow-up.
- Withdrawing from all further follow-up.

A participant may be withdrawn from trial treatment for the following reasons:

- Withdrawal of consent for treatment by the parent/carer(s)
- Intolerance to trial medication
- Any alteration in the participant's condition, which, in the opinion of the patient's treating clinician, justifies the discontinuation of the treatment.

In all instances parent/carer(s) who consented will be asked to assist a member of the research team in completing a Withdrawal Form. Parent/carer(s) do not have to contribute to completing the Withdrawal Form. However, the PI in each site should ensure that a withdrawal form is completed as fully as possible and sent to the CREAM Trial Manager for every participant that withdraws.

# 11 Trial interventions

The active medications being evaluated in this trial are well established and already widely used within their licensed indications. The active medications will not be used outside their licensed indication in the course of this trial. This is a study of their added value.

The trial has three treatment arms. Participants in all three treatment arms will receive a standard topical corticosteroid treatment for their eczema and comprehensive verbal and written eczema care instructions. All participants will also receive additional monitoring and support from a trained research nurse.

## 11.1 Treatments

### 11.1.1 Flucloxacillin suspension

The flucloxacillin suspension used in this study is manufactured by Crescent Pharma Limited and has a Medicine and Healthcare products Regulatory Agency (MHRA) Marketing Authorisation (PL 20416/0077) (Appendix V). Flucloxacillin will be supplied as granules for reconstitution in 100ml to provide a concentration of 250mg/5mL to provide multiple doses as stated in Section 11.2. Flucloxacillin will be prescribed by the patient's clinician and prepared by the Site Pharmacy as described in Section 11.4.

### 11.1.2 Erythromycin suspension

The erythromycin suspension used in this study is manufactured by Amdipharm Plc and has a MHRA Marketing Authorisation (PL 20072/0042) (Appendix II). Erythromycin will be supplied as granules for reconstitution in 140ml to provide a concentration of 250mg/5mL to provide multiple doses as stated in Section 11.2. Erythromycin will be prescribed by the patient's clinician and prepared by the Site Pharmacy as described in Section 11.4.

### 11.1.3 Fusidic acid cream

The fusidic acid cream used in this study is supplied by St Mary's Pharmaceutical Unit, Cardiff (Appendix III). Fusidic acid will be supplied as 2% cream to provide multiple doses as stated in Section 11.2. Fusidic acid will be prescribed by the

patient's clinician and prepared by the Site Pharmacy as described in Section 11.4.

### 11.1.4 Placebo suspensions

The placebos for both flucloxacillin and erythromycin suspensions used in this study are manufactured by Tiofarma BV and supplied by Mawdsleys. Placebo to flucloxacillin will be supplied as granules for reconstitution in 100ml to provide multiple doses as stated in Section 11.2. Placebo to erythromycin will be supplied as granules for reconstitution in 140mL to provide multiple doses as stated in Section 11.2. Placebo suspensions will be prescribed by the patient's clinician and prepared by the Site Pharmacy as described in Section 11.4.

### 11.1.5 Placebo cream

The placebo cream used in this study is supplied by St Mary's Pharmaceutical Unit (SMPU). Placebo cream will be prescribed by the patient's clinician and prepared by the Site Pharmacy as described in Section 11.4.

## 11.2 Treatment arms

### 11.2.1 Group 1: Oral Antibiotic and Topical Placebo

- Oral antibiotic
    - Flucloxacillin 250mg per 5mL.
        - For children aged 3 months to 2 years - 2.5mL four times a day for 7 days.
        - For children aged over 2 years to under 8 years - 5mL four times a day for 7 days.
    - OR erythromycin 250mg per 5mL if penicillin allergy
        - For children aged 3 months to 2 years - 2.5mL four times a day for 7 days.
        - For children aged over 2 years to under 8 years - 5mL four times a day for 7 days.
- Topical placebo
    - Apply cream to affected area(s) three times a day for 7 days.

### 11.2.2 Group 2: Oral Placebo and Topical Antibiotic

- Oral placebo
    - For children aged 3 months to 2 years - 2.5mL four times a day for 7 days.
    - For children aged over 2 years to under 8 years - 5mL four times a day for 7 days.
- Topical antibiotic - fusidic acid 2% cream

- Apply cream to affected area(s) three times a day for 7 days.

### 11.2.3 Group 3: Oral Placebo and Topical Placebo

- Oral placebo
  - For children aged 3 months to 2 years - 2.5mL four times a day for 7 days.
  - For children aged over 2 years to under 8 years - 5mL four times a day for 7 days.
- Topical placebo
  - Apply cream to affected area(s) three times a day for 7 days.

### 11.2.4 Treatment for all patients in groups 1, 2 and 3:

Participating clinicians will be asked to prescribe topical steroid (topical clobetasone butyrate 0.05% (Eumovate) cream or ointment (for eczema on trunk and/or limbs) and/or topical hydrocortisone 1% cream or ointment (for eczema on face)) for all the patients they refer to the CREAM trial. The treating clinician will need to choose between prescribing creams or ointments, and will be provided with guidance about best practice in relation to this decision.

## 11.3 Supply and packaging of Investigational Medicinal Product (IMP)

SMPU, which is a pharmaceutical manufacturing facility and part of the Cardiff and Vale University Health Board, will acquisition and supply flucloxacillin and erythromycin in their original packaging. Mawdsleys will acquire, manufacture and stability test the bulk placebo for both flucloxacillin and erythromycin. These products will be manufactured in accordance with Good Manufacturing Practice (GMP) and the agreement between the Sponsor and Mawdsleys. SMPU will acquisition and stability test the placebo for fusidic acid in accordance with GMP and the agreement between the Sponsor and SMPU.

SMPU will reconcile all the IMPs into sealed and labelled 'Trial Packs' in accordance with their agreement with the Sponsor. Each batch of Trial Pack undergo release by a Qualified Person (QP) at SMPU to the Site Pharmacies in Wales, South West England and Scotland.

There will be six different Trial Packs (2 per treatment group) each labelled with a unique Trial Pack number:

| Treatment Group | Treatment Pack Group Letter | IMP in Trial Pack |
|---|---|---|
| **1** | **A** | Oral active (Flucloxacillin) powder in original packaging for reconstitution to 100ml oral solution 250mg/5ml, and a labelled empty bottle; topical placebo cream (30g). |
| | **B** | Oral active (Erythromycin) powder in original packaging for reconstitution to 140mL oral solution 250mg/5ml, and a labelled empty bottle; 2 x 30g topical placebo cream. |
| **2** | **C** | Oral placebo (to Flucloxacillin) powder in a labelled bottle dispensing the reconstituted 100ml oral solution; 30g topical Fusidic Acid cream (2%). |
| | **D** | Oral placebo (to Erythromycin) powder in a labelled bottle dispensing the reconstituted 140ml oral solution; 2 x 30g topical Fusidic Acid cream (2%). |
| **3** | **E** | Oral placebo (to Flucloxacillin) powder in a labelled bottle dispensing the reconstituted 100ml oral solution; 30g topical placebo cream. |
| | **F** | Oral placebo (to Erythromycin) powder in a labelled bottle dispensing the reconstituted 140ml oral solution; 2 x 30g topical placebo cream. |

An example of other items each pack will contain:

i. Empty bottle matched to the placebo bottles.
ii. Bottle adaptor for syringe insertion.
iii. Oral delivery syringe.
iv. Labels to mark syringe for dosage variations.
v. Patient information leaflet (PIL) with instructions for use.

The primary packaging of all IMPs will state 'for clinical trial use only'. Also included on the label will be the name of the Co-chief investigators, the expiry date of the product, the batch number (relating to assembly) and a unique identifier for that tube/bottle. As the active antibiotics are being compared to placebo, to maintain blinding the IMPs will not be labelled for their content on any label on the primary or secondary packaging.

Trial materials will be stored under the conditions specified by the manufacturer (or in the Summary Product Characteristics (SmPCs)) by SMPU. Trial Packs will be distributed from SMPU to the site pharmacies as required, following a request from Site Pharmacy to the CREAM Trial Manager. Upon receipt by the Site Pharmacy, all clinical materials will be stored in a designated temperature monitored area within the pharmacy.

## 11.4 Prescribing, distribution and use of the IMP

The process of prescribing, dispensing and return of IMP is described in detail in the Pharmacy Manual.

The patient will visit their General Practice for an appointment. If their clinician (GP/Nurse Prescriber) suspect infected eczema, the clinician will complete the CREAM Prescription Form and refer the patient to the research nurse. (Erythromycin (or its placebo) will only be prescribed if the patient is known to be allergic to penicillin). The prescription will be faxed to the local trial pharmacy for preparation.

If the Site Pharmacy is dispensing flucloxacillin or erythromycin, the pharmacist will prepare the antibiotic suspension by reconstituting in the original primary packaging and decanting into a fresh bottle matched to the placebo, which will be provided in the Trial Pack.

If the clinician has prescribed the larger dosage of flucloxacillin (5mL four times a day) of oral antibiotic (or its placebo) then two identical Trial Packs will be prepared to ensure sufficient volume for a one week course.

The research nurse will collect the Trial Pack(s) from the pharmacy and deliver to the participant at the baseline visit, within 72 hours of the IMP being prescribed and on the same day that the IMP is reconstituted. The IMP will be issued to the participant at the baseline visit with instructions for use and a Patient Information Leaflet (PIL) about the potential IMP (for both active and its placebo medicine) (Appendix VI).

## 11.5 Interaction with other drugs

There is a negligible chance of interaction with other drugs. The active antibiotics are commonly used and have known safety profiles. As a precaution, listed below are medications that are known to interact with the study medication. However, it is unlikely any patient will be referred to the CREAM study if their condition requires use of the medication listed below. Any patient taking these medications will most likely not fulfil the CREAM inclusion and exclusion criteria, and therefore not be included in the study.

All participants should avoid:

- Ritonavir
- Simvastatin

Participants allergic to penicillin (who may receive erythromycin) should avoid the medicines listed below due to their interactions with erythromycin:

- Amiodarone
- Amiodarone
- Amisulpiride
- Arsenic Trioxide
- Artemther with Lumefantrine
- Atomoxetine
- Carbamazepine
- Ciclosporin
- Clopidogrel
- Clozapine
- Colchicine
- Coumarins
- Disopyramide
- Dronedarone
- Droperidol
- Ergotamine and Methysergide
- Eletriptan
- Everolimus
- Ivabradine
- Midazolam
- Mizolastine
- Moxifloxacin
- Pentamidine Isetionate
- Pimozide
- Reboxetine
- Rifabutin
- Saquinavir
- Simvastatin
- Sirolimus
- Sulpiride
- Tacrolimus
- Theophyline
- Verapamil
- Vinblastine
- Zuclopenthixol

# 12 Pharmacovigilance

## 12.1 Definitions

The following definitions are in accordance with both the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and the subsequent amendment regulations (SI2006/1938) and ICH-GCP:

### 12.1.1 Adverse Event (AE)

Any untoward medical occurrence in a clinical trial participant to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

### 12.1.2 Adverse Reaction (AR)

Any noxious and unintended response in a clinical trial participant to whom an IMP has been administered, which is related to any dose administered. A "response" to a medicinal product means that a causal relationship between a

medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

### 12.1.3 Serious Adverse Event (SAE)

Any adverse event that:

- Results in death
- Is life-threatening*
- Required hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition ***

* 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.

** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an adverse event.

*** Note: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

### 12.1.4 Serious Adverse Reactions (SARs)

Any Serious Adverse Event occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.

### 12.1.5 Suspected Unexpected Serious Adverse Reactions (SUSAR)

These are **SARs** which are classified as 'unexpected', i.e. an adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product outlined in the Investigator Brochure (IB) and SmPCs.

Example expected adverse reactions with trial treatments are listed below (and provided in detail in each medicine's SmPC):

- *Oral erythromycin*

| Disorder | Examples |
|---|---|
| Blood and lymphatic system | Eosinophilia |
| Cardiac | QTc interval prolongation, torsades de pointes, palpitations, and cardiac rhythm disorders including ventricular tachyarrhythmias |
| Ear and labyrinth | Deafness, tinnitus<br>(There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency or taking high doses.) |
| Gastrointestinal | Upper abdominal discomfort, nausea, vomiting, diarrhoea, pancreatitis, anorexia, infantile hypertrophic pyloric stenosis,Pseudomembranous colitis |
| General disorders and administration site conditions | Chest pain, fever, malaise |
| Hepatobiliary disorders | Cholestatic hepatitis, jaundice, hepatic disfunction, hepatomegaly, hepatic failure, hepatocellular hepatitis |
| Immune system disorders | Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis |
| Investigations | Increased liver enzyme values |
| Nervous system disorders | Isolated reports of transient central nervous system side effects including confusion, seizures and vertigo. (A cause and effect relationship has not been established.) |
| Psychiatric disorders | Hallucinations |
| Renal and urinary disorders | Interstitial nephritis |
| Skin and subcutaneous tissue disorders | Skin eruptions, pruritus, urticaria, exanthema, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| Vascular disorders | Hypotension |

- *Oral flucloxacillin*

| Disorder | Examples |
|---|---|
| Blood and lymphatic system | Neutropenia (including agranulocytosis), thrombocytopenia, haemolytic anaemia. |
| Immune system | Anaphylactic shock (exceptional with oral administration),angioneurotic oedema |
| Gastrointestinal | Minor gastrointestinal disturbances, Pseudomembranous colitis |
| Hepato-biliary | Hepatitis and cholestatic jaundice |
| Skin and subcutaneous tissue | Rash, urticaria and purpura<br>Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis |
| Musculoskeletal and connective tissue | Arthralgia , myalgia |
| Renal and urinary | Interstitial nephritis |
| General disorders and administration site conditions | Fever |

- *Topical fusidic acid*

| Disorder | Examples |
|---|---|
| Immune system | Hypersensitivity |

| | |
|---|---|
| Eye | Conjunctivitis |
| Skin and subcutaneous tissue | Pruritus, rash including erythematous, maculo-papular and pustular reactions, contact dermatitis, irritation at site of application (including pain, stinging, burning and erythema). |

## 12.2 Causality

Most adverse events and drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

| **Relationship** | **Description** |
|---|---|
| **Unrelated** | There is no evidence of any causal relationship |
| **Unlikely** | There is little evidence to suggest there is a casual relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment). |
| **Possible** | There is some evidence to suggest a causal relationship (e.g. because the event occurs within one week after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments). |
| **Probable** | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| **Definitely** | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |
| **Not assessable** | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship. |

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigator(s). The pharmaceutical companies and/or other clinicians may be asked to advice in some cases.

The assignment of the causality should be made by the Investigator responsible for the care of the participant.

The Chief Investigator (or Clinical Reviewer Delegate) will also be responsible for making an assessment of causality.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the local site investigator/PI's views will prevail and the MHRA will be informed of this view.

## 12.3 Expectedness

The assessment of whether or not an Adverse Reaction is an expected reaction from the administration of the IMP will be provided by the Chief Investigator (or Clinical Reviewer Delegate), it will not be provided by the Investigator responsible for the care of the participant.

This assessment will be based on the approved Reference Safety Information for the IMP indicated.

## 12.4 Reporting procedures

Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures. The reporting procedure is depicted graphically in the flowchart Figure 2.

### 12.4.1 Non serious AR/AEs

Potential side effects will be recorded in the participant's dairy over the first 4 weeks of their participation. The parent/carer(s) will completed the diary and highlight the severity of any non-serious AR/AEs.

### 12.4.2 Serious AR/AEs

Fatal or life-threatening SAEs and SUSARs should be reported to the Trial Manager within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcomes and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. An SAE form should be completed and faxed to the study coordination centre for all SAEs within 24 hours. Additional information should be sent within 5 days if the

reaction has not resolved at the time of reporting. SAE reporting and processing procedures will be included in the training of all sites and research site staff.

**No assessment of expectedness will be provided by the Investigator responsible for the care of the participant.**

### 12.4.3 SUSARs

In the case of serious, unexpected and related adverse events, the staff at the site should:

Complete the SAE case report form and send it immediately (within 24 hours, preferably by fax), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.

**OR**

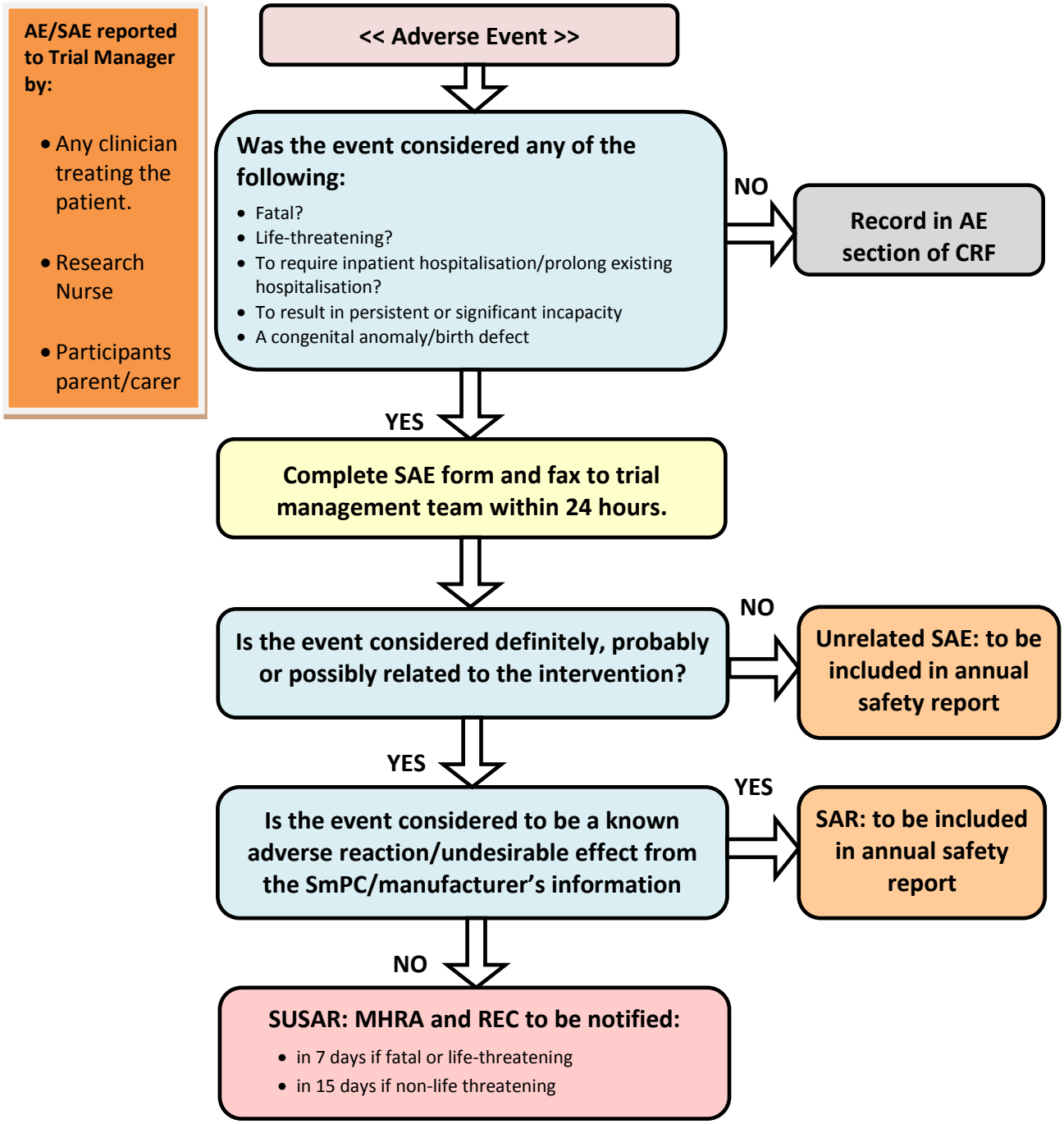
Contact the CREAM Trial Manager by phone and then send the completed SAE form to the study coordination centre by fax within the following 24 hours as above.

The study coordination centre will notify the MHRA and main Research Ethics Committee (REC) of all SUSARs occurring during the study according to the following timelines, **where day zero is defined as the date the SAE form is initially received at SEWTU:**

- SUSARs which are fatal or life-threatening must be reported not later than 7 calendar days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 calendar days.
- SUSARs that are not fatal or life-threatening must be reported within 15 calendar days of the sponsor first becoming aware of the reaction.

Local investigators should report any SUSARs and/or SAEs as required by their Local REC and/or Research and Development Office.

**Figure 2: Flowchart for Adverse Event Reporting Procedures**




**Contact details for reporting SAEs and SUSARs**

**Fax: 029 2068 7612,**
**for attention of CREAM TRIAL MANAGER, Dr Inaam-ul Haq**
**Please send SAE forms to:**
**South East Wales Trials Unit (SEWTU)**
**School of Medicine, Cardiff University**
**7th floor, Neuadd Meirionnydd**
**Heath Park**
**Cardiff, CF14 4YS**
**Tel: 029 2068 7665 (Mon to Fri 09.00 – 17.00)**

# 13 Trial procedures

## 13.1 Training of staff

All staff involved in the trial specific procedures (including recruitment/consent, collection of trial data, application of interventions and clinical assessments) will be trained in GCP.

### 13.1.1 Training of research nurses

The research nurses involved in the clinical aspects of this trial will be selected by the PIs of each region, who will ensure that they have the relevant skills, qualities and experience and up-to-date GCP training.

Prior to recruiting participants, the research nurses will attend a trial-specific workshop, which will include training in practical assessment of children with eczema, the IMP prescribing and dispensing procedure (how to receive, log and process patient's referred from general practices), assessing eligibility, informed consent procedures, taking swabs and training parents in taking swabs; and data collection procedures (including administering the validated outcome measures). An example of the planned training programme is provided in Appendix VII.

### 13.1.2 Training of staff at sites

Clinicians at sites will receive training to ensure they understand the CREAM protocol and how to refer patients using Trial Torrent or by contacting the research nurse directly. All staff at the sites with delegated responsibility for any aspect of the CREAM study will be provided suitable training to ensure they understand the referral procedure.

Practices using Trial Torrent will have remote support and local researcher assistance to ensure suitable data collection and referral of patients by sites.

### 13.1.3 Training of staff at Site Pharmacies

Staff at Site Pharmacies will work in accordance to their Standard Operating Protocols (SOPs) to receive, store and dispense the Trial Packs. All Site Pharmacies will be initiated formally during which training will be provided for relevant trial-specific SOPs to explain prescription handling, pharmacovigilance and Trial Pack handling.

## 13.2 Data collection/assessments

The schedule for timing, frequency and method of collection of all trial data is summarised in Table 1. Assessments will be performed as close as possible to the required time point.

Where an assessment cannot be performed within a reasonable timeframe around the required time point, this will be documented in the research nurse log and/or participant's CRF, including the reason for missing the assessment (e.g. parent cancelled appointments).

## 13.3 Baseline assessments

Once the patient is referred to the research nurse, the research nurse will contact the parent/carer(s) to arrange an appointment for the baseline visit at their home (or other suitable location). Prior to the baseline assessment, the research nurse will attend the Site Pharmacy and collect the Trial Pack(s) for that participant.

Once informed consent has been obtained the research nurse will:

1. Register the participant and their parent/carer(s) to the trial.
2. Conduct a standardised interview with the parent/carer(s).
3. Conduct a standardised examination of the child, including assessment of the EASI score.
4. Ask the parent/carer(s) to complete the POEM, IDQoL/CDQLI, DFI outcome measures, the resource use (as shown in Table 1) and the health utility (see Section 10.3) instrument.
5. Take swab samples from the child's infected eczema, nose and mouth.
6. Provide the parent/carer(s) with the study medication, and provide instructions on use of study medication.
7. Provide the parent/carer with standardised advice about caring for a child with eczema.
8. Give the parent/carer(s) a four-week symptom diary and provide them with instructions on diary completion.

The research nurse will arrange to re-visit the participant and their parent/carer(s) at 2 and 4 weeks following their initial visit. The research nurse will also advise parent/carer(s) that there will be telephone and postal follow-up at 3 months, and that the parent/carer(s) will be asked to take swab samples from the participant (infected eczema, nose and mouth) at 3 months and 12 months.

**Table 1: Table Summary of data collection**

| Time Point | Baseline Evaluation | Follow Up Period | | | | |
|---|---|---|---|---|---|---|
| | | 2 weeks | 4 weeks | 4 Week Diary | 3 months | 12 months |
| Data Method of Collection | Face-to-face | Face-to-face | Face-to-face | Completed daily by parents | Questionnaire/telephone + postal swabs | GP medical record search + postal swabs |
| Demographics, presenting features | X | | | | | |
| Swab eczematous skin | X | X | | | X | X |
| Swabs anterior nares and oropharynx | X | X | | | X | X |
| POEM | X | X | X | | X | |
| EASI | X | X | X | | | |
| IDQoL/CDLQI | X | X | X | | X | |
| DFI | X | X | X | | X | |
| Health utility (see Section 10.3) | X | X | X | | X | |
| Medication use | | | | X | | |
| Parental preference for treatment | | | | | | |
| Daily symptoms | | | | X | | |
| Adverse effects | | X | | X | | |
| Resource use | X | | X | X | X | X |
| Consultations and antibiotic use for eczema | | | | X | | X |

*Weigh unused medication

## 13.4 Follow-up assessments

The research nurse will re-visit participants and their parent/carer(s) at 2 and 4 weeks following the initial visit. The nurses will make every effort to visit at these exact time points, but if for any reason it is not possible to visit on the exact follow-up dates then they will be asked to visit as close as possible to the date in question within the thresholds: 2 week visit, -1/+3 days; and 4 week visit, -3/+3 days. There will be telephone and postal follow-up at 3 months and a medical–record search at 12 months. Swab samples (infected eczema, nose and mouth) will be collected at 2 weeks, 3 months and 12 months and returned in postage-paid packaging to the Specialist Antimicrobial Chemotherapy Unit (SACU), Cardiff.

### 13.4.1 Week 2: Research nurse visit

The research nurse will record medication use and collect any unused study medication and provide ongoing support for the parent/carer(s); collect data for the outcome measures (EASI, POEM, IDQoL/CDLQI, DFI, and health utility (see Section 15.4); and collect the first 2 weeks data from the symptom diary. The RN will provide the parent/carer(s) with training in taking the swabs. Swabs will again be collected from the infected eczema, nose and mouth of the participating child and returned in postage-paid packaging (Section 13.5).

### 13.4.2 Week 4: Research nurse visit

The research nurse will provide ongoing support for the parent/carer(s); collect information for the outcome measures (POEM, EASI, IDQoL/CDLQI, DFI, and health utility (see Section 10.3)); collect the final 2 weeks of the 4 symptom diary; and ask parent/carer(s) two short questions regarding any difficulties they may have had answering the health utility questions.

### 13.4.3 Month 3: Telephone and postal follow-up

Three months following the recruitment of each participant, the parent/carer(s) will be contacted by letter, requesting that they take and return the 3-month swab samples. As a reminder to take and return the swabs at 3 months, parent/carer(s) will have swabs and postage-paid packaging posted with instructions on taking, handling and postal return of the swabs (Section 13.5).

Parent/carer(s) will also be send postal questionnaires to complete. This will involve completing information for outcome measures (POEM, IDQoL/CDLQI, DFI, and health utility (see Section 10.3)), and answering some questions about resource use.

If the questionnaire and/or packaging is not returned within 1 week, the research team will conduct telephone interviews. The interviewer will also encourage collection of the 3-month swab samples (Section 13.5).

### 13.4.4 Month 12: Mouth and nose swabs

Twelve months following the recruitment of each participant, the parent/carer(s) will be contacted by letter, requesting that they take and return the 12-month swab samples. Parent/carer(s) will have swabs and postage-paid packaging posted to them as a reminder to take and return the swabs at 12 months (Section 13.5). If the sample is not returned within 1 week, the research team will telephone the parent/carer(s) to remind them.

### 13.4.5 Month 12: Medical Record search

Data will be extracted from the primary care medical records for each participant for the 12-month period following recruitment. GP practices will be visited by a member of the research team or a clinical study officer or research nurse working for the local research network; or be asked to conduct a search of their practice records and send them to the study team at 12 months following recruitment of their last participant. The record search will be used to identify healthcare consultations (primary and secondary care), drugs prescribed, subsequent episodes of infected eczema, and use of antibiotics for the infected eczema.

## 13.5 Collection of swab samples

Swabs will be collected at baseline, 2 weeks, 3 months, and 12 months. Swabs will be taken from suspected infected eczema to identify *S. aureus* or Group A Streptococcus infection, nasal swabs for *S. aureus* carriage, and oral swabs to identify any change in frequency of penicillin or macrolide resistance in Group A Streptococcus commensal flora. Research nurses will take the baseline and 2-week swabs and parent/carer(s) will be asked to take the swabs at 3 months and 12 months.

The research nurses will provide parent/carer(s) with training in taking swabs during the 2-week visit. Parent/carer(s) will be sent a postal reminder and packaging at 3 months and 12 months. Parent/carer(s) will be provided with swabs, a postage-paid packaging for returning the swabs, and written instructions on collecting them, prior to these two collection points.

The research nurse or delegated member of the research team will contact the parent/carer(s) who have not returned the swabs by telephone in order to remind them to do so. In addition, if the parent/carer is contacted by the research team

about the questionnaire or contacts the research team for any other reason, the researcher will again encourage collection of the specimens. Collection of nasal swabs is likely to be the most difficult for the carers. In addition to providing training, we will be using short swabs that cannot be inserted too far into the nose. Such an approach has been shown to be feasible in other studies [23], even when this involves deeper swabbing (from the turbinates) [24].

### 13.6 Microbiology processing

The Specialist Antimicrobial Chemotherapy Unit (SACU) in Cardiff will receive the samples and log the date and time of receipt of the three different samples alongside the Patient ID and Date of Birth.

Nasal swabs will be cultured and any *S. aureus* will be confirmed and semi quantitative counts determined along with antimicrobial susceptibilities.

Infected eczema swabs will be cultured and *S. aureus* and Streptococci identification/grouping will be confirmed and semi quantitative counts determined along with antimicrobial susceptibilities.

Oropharyngeal swabs will be cultured and any streptococcus species found on non-selective and antimicrobial selective media will be confirmed and quantitative counts determined.

All isolates will be stored at -80°C storage. SACU will enter data into their own database which will be transferred securely to the Data Manager every month and merged with the CREAM database. To ensure all samples are returned at their required time points, SACU will inform the Trial Manager or Data Manager within 24 hours of receiving samples. The Data Manager will monitor the return of swabs and follow up with parent/carer(s) if any swabs are missing. Further details of the microbiology process, will be defined in a study-specific microbiology manual.

## 14 Statistical considerations

### 14.1 Randomisation

The study statistician will prepare randomisation tables for the randomisation of sites (General Practices) (for use of Trial Torrent) and participants. Further details of the randomisation process are provided in the randomisation protocol.

## 14.2 Primary Outcome Measure

The primary outcome will be an assessment of subjective severity at two weeks as measured using the validated Patient-Oriented Eczema Measure (POEM) [25]. The POEM is based on symptoms over the previous week and therefore will be measuring symptom severity during the week following the end of experimental treatment, the period when a treatment effect is most likely. We have chosen a subjective measure for our primary outcome in recognition of the importance of measuring effects that are of importance to patients. POEM has been shown to be valid and reliable, easy to complete, sensitive to change, and is recommended for use in trials of AD [26].

## 14.3 Secondary Outcome Measures

Subjective eczema severity will also be measured using the POEM at 4 weeks, and 3 months. Objective eczema severity will be measured using the Eczema Area and Severity Index (EASI) [27]. Quality of life will be assessed using the Infants Dermatology Quality of Life instrument (IDQoL) [28] (for children aged 3 months to under 4 years old) and Children's Dermatology Life Quality Index (CDLQI) [29] (for children aged 4 years to under 8 years), and impact on the family will be measured using the Dermatitis Family Impact (DFI) instrument [30]. These are both well-validated, short, easy to use instruments, and we have expertise in our team in using them. A four-question condition-specific, preference-based measure of health for children [31] will be used for the exploratory cost utility analysis.

A daily diary will be used to record symptom severity, medication use, carers' preference for treatment (recorded at 2 weeks), and healthcare resource use during the first 4 weeks. The diary will record the following symptoms each day: carer's assessment of overall severity, itch, sleep disturbance, oozing or weeping, bleeding, fever, and possible adverse effects (nausea, vomiting, diarrhoea, abdominal pain, joint pains, and new rash). We will pilot this diary with a sample of carers prior to use in the trial. We have had success in using daily symptom diaries in a number of studies, including four-week diaries [32], and diaries completed by parents/carer(s) [33] [34]. One study successfully collected daily diary data from the majority of parents/carers for eight weeks [35]. There is also evidence for the reliability and validity of diary data recorded by parents/carer(s) [36].

### 14.4 Sample size calculation

Studies comparing active eczema treatments with placebo have generally found large effect sizes (>0.7). There are no data available on the likely effect size identified by POEM. In a study of children with 'moderate to severe eczema'[14] the median baseline POEM score was 13 (out of 28). Assuming a clinically important difference of 3 on the POEM score and a common standard deviation of 7, we estimate a meaningful effect size of 0.429. The main analysis will be a comparison of each active treatment with placebo. Therefore, using a significance of 0.025 (to allow for two comparisons), with 90% power, we would need 137 participants per treatment group (total 411). Allowing for 20% loss to follow-up we aim to recruit 516 participants (172 per centre).

## 15 Analysis

### 15.1 Main analysis

The primary analysis will be an intention to treat analysis comparing POEM scores at two-weeks in the treatment groups with active medicine with those in the placebo only group. We will do this using ANCOVA, controlling for baseline POEM score. This approach makes certain assumptions about the data, which will be tested prior to analysis. If the data do not fit with these assumptions then we will use a non-parametric approach. Further detail will be provided in the Statistical Analysis Plan.

### 15.2 Secondary analyses

We will also:

- Create a binary success/failure score based on what is deemed a clinically important change in POEM score (both absolute and percentage changes will be investigated and an appropriate method chosen), which will be analysed using logistic regression, controlling for important patient characteristics.
- Conduct a Complier Average Causal Effect (CACE) analysis (this approach is recommended over a per-protocol analysis http://www.hta.ac.uk/fullmono/mon1143.pdf) and an analysis adjusted for age, sex, and presence and resistance characteristics of *S. aureus* on skin swab at baseline. Differences in EASI scores IDQoL/CDLQI scores and DFI scores will be assessed using the same approach.

- Explore the rate of recovery using data from the daily symptom diaries. We will compare time to recovery using survival analysis based on the carers' reported 'day recovered' and compare the rate of change of a total daily symptom score in the three groups.
- Describe parent/carer(s)' preference for treatment (cream or oral suspension). Differences in preference between the three groups will be compared using a chi-squared test.
- Describe prevalence of specified organisms and resistance among those organisms (as percentages with 95% confidence intervals). The research team will describe the prevalence of *S. aureus* isolates from swabs of infected eczema, and methicillin and fusidic acid resistance amongst those isolates, in each group at baseline, 2 weeks, 3 months, and 12 months. In addition to presenting crude proportions, in the 3 and 12-month analyses the research team will adjust for subsequent courses of antibiotics. Furthermore, in order to describe the effect of each treatment on the development of resistant organisms, the research team will describe the prevalence of methicillin and fusidic acid resistance in *S. aureus* isolates from the anterior nares, and the prevalence of resistance to oxacillin and erythromycin in *S. pneumoniae* isolates from the oral cavity, at the same time points.
- An exploratory analysis will investigate the effectiveness of erythromycin compared with flucloxacillin.

## 15.3 Missing data

Every effort will be made to avoid missing data. Nurses will be trained in data collection and the questionnaires filled out by them will be designed to minimise the amount of missing information possible. Missing data, where it does occur, will be investigated in order to determine the most appropriate strategy for dealing with it. The proposed strategies are: mean value imputation, last observation carried forward (potentially useful for missing diary data), as well as multiple imputation. Complete case analysis will also be presented so that the impact of missingness can be assessed. The main CACE analysis allows for the presence of missing data also.

## 15.4 Economic analysis

The primary economic evaluation will be in the form of a cost effectiveness analysis (CEA) assessing total costs against the primary outcome (POEM).

The CEA will adopt a societal perspective. Parent/carer(s) time off work will be collected via additional questions to parent/carer(s) at the 4 week and 3 month follow-up points. All contacts with primary care (surgery consultations and home visits) and secondary care (including accident and emergency attendances, inpatient admissions and outpatient visits) and all drugs prescribed between baseline and 12 month follow-up will be collected from GP records at 12 months. All resources will be valued using standard methods [37]. Unit costs will be mainly from national sources [38].

Mean differential costs will be estimated and assessed against mean POEM scores. As cost data are often skewed, tests for normality will be applied. If distributions are shown to be non-normal, non-parametric bootstrapping methods will be used to test for mean cost differences between groups [39]. This approach will identify if any of the 3 treatments dominates (lower cost/higher effect) and is hence unambiguously the most cost effective. In the case of non-dominance, results will be reported as incremental cost effectiveness ratios showing the extra cost of achieving one extra unit of effect. A series of one way and multivariate sensitivity analyses will be undertaken to assess how sensitive results are to changes in the assumptions used.

The absence of published economic evaluations with POEM as the unit of effectiveness means that the cost effectiveness of oral/topical antibiotics relative to other treatments for eczema cannot be assessed. The study will, however, provide a benchmark for future studies i.e. any treatment with a cost per unit of POEM below those determined within CREAM will be more cost effective than oral/topical antibiotics.

Cost utility analysis (CUA) is the type of economic evaluation preferred by the National Institute for Health and Clinical Excellence (NICE) [40]. CUA however, requires single index preference-based measures of health related quality of life to generate Quality Adjusted Life Years (QALY). Such analyses can produce incremental cost utility ratios (extra cost per extra QALY), which can then be assessed against the NICE threshold (currently £30,000 per extra QALY) to determine if the intervention is cost effective.

Given that participants in the CREAM study will be aged below 8 years, use of CUA as the main economic evaluation would be problematic. A recent systematic review of generic health related quality of life measures in children under 5 years

old concluded that none of the existing generic measures was both psychometrically and conceptually robust [41].

However, the Sheffield Health Economics Group has recently developed a condition specific preference-based HRQoL measure for children with atopic dermatitis [31], which is capable of generating QALYs but has not to date been tested within a clinical trial. CREAM provides an opportunity to test the new measure.

The economics of CREAM will thus also include an exploratory cost utility analysis. The study will attempt to identify the minimum age with which the new measure can be used. This will be done by:

1) Comparing the standard errors in responses by carers of children aged under X years with those above aged X years (X to be varied). The greater sensitivity of the measure when applied to older children should be reflected in lower standard errors.
2) As part of the 4-week face-to-face data collection parent/carer(s) will be asked two short questions to determine how difficult/meaningful they found the health utility questions. Responses from parents of younger/older children sub-groups will be compared.

While this element of the study will primarily be methodological development, exploratory incremental cost utility ratios will be produced using only NHS and personal social services costs as recommended by NICE for cost utility studies. Probabilistic techniques used to produce cost effectiveness acceptability curves showing the probability of the intervention falling below a range of wiliness to pay thresholds e.g. the £30,000 per extra QALY used by NICE.

# 16 Data storage & retention

All research data will be kept until the youngest participant has reached the age of 21 or 15 years after completion of the trial (whichever is longer), in line with Cardiff University's Research and Development Framework guidance for clinical research. Archiving and access to archive will be managed in accordance with the standard operating procedures of the UK Clinical Research Collaboration (UK CRC) registered South East Wales Trial Unit (SEWTU). Electronic data will be stored confidentially on password-protected servers maintained on the Cardiff University Network. Paper records will be stored in appropriately labelled files in secure storage cabinets.

# 17 Trial closure

For the purpose of regulatory and ethical requirements the end of the trial is defined as the date of the last data capture for the last participant undergoing protocol treatment.

Trial recruitment will end when 516 participants have been randomised, or at the request of the Trial Steering Committee or Independent Data Monitoring Committee.

# 18 Regulatory issues

## 18.1 MHRA Compliance

This trial has Clinical Trials Authorisation from the UK Competent Authority: MHRA. Reference 21323/0035/001-0001.

The sponsor, Cardiff University, will determine the level of monitoring required after assessing risk together with SEWTU. The trial will be conducted to International Conference on Harmonization Good Clinical Practice (ICH GCP). A EudraCT number and MHRA Clinical Trials Authorisation (CTA) will be obtained. We will meet all regulatory requirements to report adverse events, in particular Suspected Unexpected Serious Adverse Reactions (SUSARs). The Trial Manager will report SUSARS to the MHRA within 7 days for life-threatening and 15 days for non-life-threatening. Roles and responsibilities will be set ahead of Trial commencing. Trial drugs (branded pharmaceuticals and placebos) will be manufactured according to Good Manufacturing Practice (GMP) by the supplier of the branded products and placebo manufacturer, labelled according to Annex 13 and supervised and distributed by a Qualified Person (QP). All the staff involved in the Trial will be GCP trained and drug accountability logs maintained.

## 18.2 Ethical approval and Research Governance

The CREAM trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18$^{th}$ World Medical Assembly, Helsinki 1964 and later revisions.

Ethical approval was granted (Ref: 12/WA/0180) from the Multi-Centre Research Ethics Committee for Wales of the National Research Ethics Service via the Integrated Research Application System (IRAS). R&D approvals will be sought from the respective NHS Health Boards in Wales, England and Scotland. Clinical

Trial Authorisation will be sought from the Medicines and Healthcare products Regulatory Agency.

CREAM will be conducted according to the principles of good research practice (including proper and appropriate conduct of research, professional integrity, honesty, statistical methods, use of data interpretation of data, non plagiarism) and the Research Governance Framework for Health and Social Care. The Trial will comply with NHS Ethics Committees and Health and Safety regulations.

The Trial team will ensure all reports required to be submitted to the HTA and/or MHRA are completed and received within the specified time points (i.e. progress reports, annual reports, SUSAR reports, early termination/end of the Trial). Any substantial changes to the Trial will be sent to the HTA and/or MHRA for approval and non-substantial sent as notification only.

Full written consent will be obtained from those legally allowed to consent on children's behalf, and all research staff with participant contact will have passed Criminal Records Bureau checks.

All research data will be handled according to the principles of the Data Protection Act, especially for sensitive, personal data. Data will anonymised and stored on a password protected computer located in secure University buildings and appropriately backed up.

## 18.3 Consent

The study participants are young children (three months to less than eight years of age), and the parent/carer(s) will be asked to give written informed consent on behalf of their child for their child to take part in the study.

The study nurse will work closely with the parent/carer(s) to ensure appropriate consent to participation. The parent/carer(s) of children and the children will be informed about the trial through the Participant Information Sheet (PIS), pictorial booklets supplemented by verbal explanations from the research nurses. Randomisation (chance of receiving one of the trial arms), placebo and blinding will be explained in understandable terms in the PIS, which will be re-enforced by the trained research trial nurses. The PIS will also include details of any potential effects of not receiving an antibiotic along with the risks and benefits of the trial. All parent/carer(s) or those legally allowed to consent for the participants will be asked to provide written, informed consent before the trial commences. The parent/carer/legal representative(s) will be given as much time as they require to

ask questions and decide whether or not they would like their child to take part in the trial. Consent will only be considered informed following provision of adequate participant information.

The Trial Manager based in SEWTU will work closely with clinicians and research nurses to facilitate recruitment and appropriate administration of parent/carer(s) and participant information and consent documentation.

Any parent/carer(s) who does not consent to their child's participation in the trial will be made aware that not taking part will have no detrimental impact on their or their child's current and future healthcare and treatments. The parent/carer(s) will be made aware that they can withdraw their child at any stage without prejudice, and that withdrawal will have no detrimental impact on current and future treatments and health care.

## 18.4 Confidentiality

The Chief Investigators and the CREAM research team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998. All data will be handled according to the principles of the Data Protection Act, especially for sensitive and personal data. Data will be anonymised and stored on a password-protected computer located in secure University buildings and appropriately backed up. Any data transfer across participant organisations will be closely monitored by a designated member of the trial team. A privacy risk assessment in each centre (Cardiff, Dundee and Bristol) will proactively identify and ameliorate risks of breaches of confidentiality and clearly designate the named individuals who will be allowed access to identifiable information. Published outcomes of the trial will not enable identification of the individual participants. All data will be retained for up to 15 years post trial closure in line with Cardiff University's procedures.

## 18.5 Trial Indemnity

Cardiff University will provide indemnity and compensation in the event of a claim by, and on behalf of participants, for negligent harm as a result of the study design and/or in respect of the protocol authors/research team. Cardiff University will not provide compensation for non-negligent harm.

The study will be conducted in accordance with SEWTU generic and study-specific operating procedures (SOPs) and work instructions. All trial related staff will be trained in those aspects of Good Clinical Practice (GCP) appropriate to their role in

the trial. Research Nurses will be trained in appropriate aspects of GCP (in particular, the informed consent process). The trial manager will visit the study sites to review compliance with the study protocol.

All applicants and clinical staff employed in a role that affects patient care will hold honorary contracts with the appropriate Health Board, conferring the protection of the NHS clinical negligence arrangements for staff.

Delegated responsibilities will be assigned to the NHS organisations taking part in this study.

### 18.6 Trial Sponsorship

Cardiff University will act as sponsor for the trial. Delegated responsibilities will be assigned to the NHS Trusts and collaborating institutes (university of Dundee and University of Bristol) taking part in this trial.

### 18.7 Funding

The CREAM trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (HTA Ref: 09/118/03).

### 18.8 Audits & inspections

The trial is participant to inspection by the NIHR as the funding organisation. The study may also be participant to inspection and audit by Cardiff University under their remit as sponsor, and the MHRA.

## 19 Trial management

### 19.1 Trial Management Group (TMG)

The TMG will consist of the Chief Investigators, co-applicants and collaborators, Trial Manager, Trial Statistician and Trial Administrator. The role of the TMG is to help set up the trial by providing specialist advice, input in and comment on the trial procedures and documents (PIS, protocol etc) and advise on the promotion and the running of the trial. The group will meet monthly during the trial. This group will also review and advise on the reporting of SAEs. Additional meetings will be held on specific topics during the set-up phase covering data management and research nurse/clinical study officer training.

TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

### 19.2 Project Team (PT)

This group will consist of members of the study team involved in the day-to-day conduct of the trial, and will include the Chief Investigators, Principal investigators, Trial Manager, Trial Statistician and Trial Administrator. The group will meet weekly to discuss the day-to-day issues that arise from the trial. Important discussions will be relayed to the TMG to for a final decision.

### 19.3 Trial documentation and data

Electronic data will be stored in fire-walled University computers. All files will be password protected and only accessible to designated researchers involved in the trial. All procedures for data storage, processing and management will be in compliance with the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to designated members of the research team. The trial statistician will carry out analysis. All essential documents generated by the trial will be kept in the trial master file.

## 20 Data monitoring & quality assurance

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.

### 20.1 Trial Steering Committee (TSC)

A TSC, consisting of an independent chair, and two other independent members including a patient representative, will meet at least annually. The first meeting will be before the trial commences to review the protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The Trial Manager and statistician will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC.

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

### 20.2 Independent Data Monitoring Committee (IDMC)

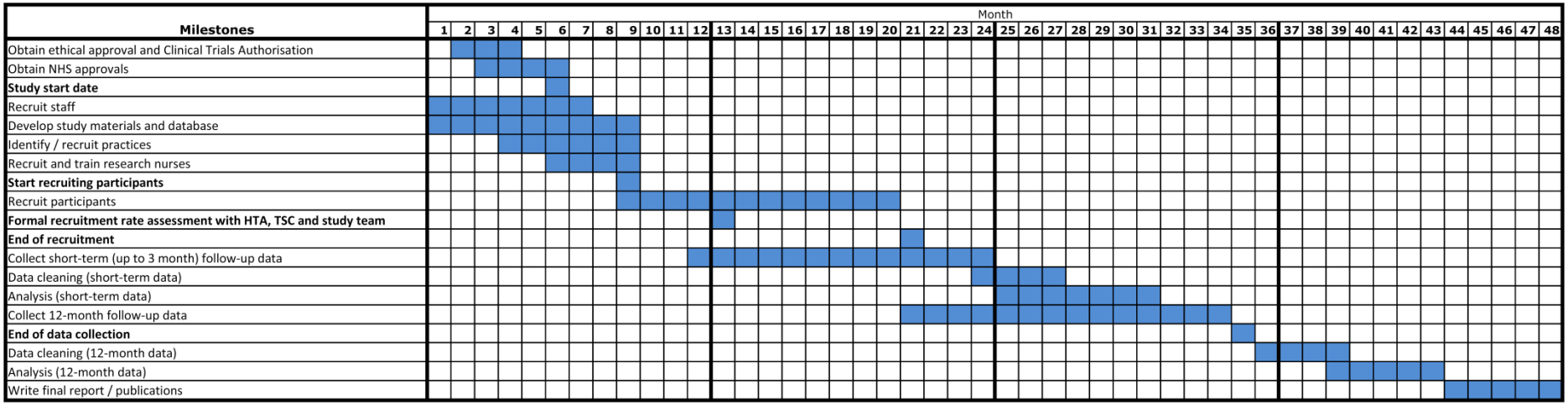
An IDMC will be established and will meet at least annually. The Committee will consist of an independent chair and two/three other independent members. The first meeting will take place before the Trial commences in order to review the protocol and agree on timelines for interim analyses to take place. The main role of the IDMC is to review the data periodically and makes recommendations to the TSC.

## 21 Publication and dissemination policy

All publications and presentations relating to the study will be authorised by the Trial Management Group. In addition to the required final report and monograph for the HTA Programme, we will publish the main trial results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and lay representatives we will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the study results into clinical care. This will include presentations at meetings and written executive summaries for key stakeholder groups such as Primary Care Trusts and General Practices, Royal Colleges, Medical Schools, and relevant patient groups.

The first publication of the trial results will include at least the trial's Chief Investigators, Statistician and Trial Manager as authors. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Trial Coordination Centre.

# 22 Milestones



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# 24 Appendices

- **Appendix I: The UK Working Party's Diagnostic Criteria for Atopic Eczema**
- **Appendix II: SmPC for Erythromycin**
- **Appendix III: SmPC for Fusidic Acid**
- **Appendix IV: Potency of a topical corticosteroid preparation**
- **Appendix V: SmPC for Flucloxacillin**
- **Appendix VI: Example Patient Information Leaflet (PIL) for Trial Packs**
- **Appendix VII: Example of training: Research Nurse Training Day**

# Appendix I

## The UK Working Party's Diagnostic Criteria for Atopic Eczema

The UK working party criteria state that in order to qualify as a case of atopic eczema with the UK diagnostic criteria, the child MUST have:

- An itchy skin condition (or parental report of scratching or rubbing in a child), plus three or more of the following:
    - History of involvement of the skin creases, such as folds of elbows, behind the knees, front of ankles or around the neck and/or cheeks.
    - A personal history of asthma or hay fever (or history of atopic disease in the first degree relative in those under 4 years).
    - A history of a generally dry skin in the last year.
    - Visible flexural dermatitis (or dermatitis involving the cheeks/forehead and outer of the limbs in children under the age of 4 years).
    - Onset of rash under the age of 2 years (not used in children below the age of 4 years).

# Appendix II

## SmPC for Erythromycin

# Appendix III

## SmPC for Fusidic Acid

# Appendix IV

## Potency of a topical corticosteroid preparation

Potency of a topical corticosteroid preparation is a result of the formulation as well as the corticosteroid. Therefore, proprietary names are shown below as described in the British National Formulary (BNF) No.62 [42]:

| Proprietary names | Generic name/active ingredient(s) | Potency |
|---|---|---|
| Dermovate | clobetasol propionate | Very Potent |
| Nerisone Forte | diflucortolone valerate | Very Potent |
| | Clobetasol propionate with neomycin and nystatin | Very potent with antimicrobials |
| Bettamousse | betamethasone valerate | Potent |
| Betnovate | betamethasone valerate | Potent |
| Cutivate | fluticasone propionate | Potent |
| Diprosone | betamethasone dipropionate | Potent |
| Elocon | mometasone furoate | Potent |
| Locoid/Locoid Crelo | hydrocortisone butyrate | Potent |
| Metosyn | fluocinonide | Potent |
| Nerisone | diflucortolone valerate | Potent |
| Synalar | fluocinolone acetonide | Potent |
| Aureocort | triamcinolone acetonide and chlortetracycline hydrochloride | Potent with antimicrobials |
| Betnovate-C | betamethasone valerate and clioquinol | Potent with antimicrobials |
| Betnovate-N | betamethasone valerate and neomycin sulphate | Potent with antimicrobials |
| Fucibet | fusidic acid and betamethasone valerate | Potent with antimicrobials |
| Lotriderm | betamethasone and clotrimazole | Potent with antimicrobials |
| Synalar C | fluocinolone and clioquinol | Potent with antimicrobials |
| Synalar N | fluocinolone and neomycin | Potent with antimicrobials |
| Diprosalic | betamethasone dipropionate with salicylic acid | Potent with salicylic acid |

# Appendix V

## SmPC for Flucloxacillin

# Appendix VI

## Example Patient Information Leaflet (PIL) for Trial Packs

# Appendix VII

## Example of training: Research Nurse Training Day