The Best Emollient for Eczema (BEE) trial: a randomised trial comparing the effectiveness of four types of commonly prescribed emollients for children with eczema

Trial Protocol

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1 Table of contents

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3 Study synopsis

Study title	The Best Emollient for Eczema trial
Short title	The BEE study
Clinical phase	IV
Study design	Pragmatic, multi-centre, individually randomised, parallel group superiority trial of four types of emollients in children with eczema, with internal pilot and nested qualitative study.
Setting	Primary care (GP practices)
Study participants	Children with mild, moderate or severe eczema
Purpose of trial	To compare the effectiveness and acceptability of four different types of emollient commonly used to treat eczema
Primary objective	To compare the medium-term (16 weeks) effectiveness of the four types of emollients in children with eczema with respect to patient-reported eczema symptoms
Secondary objectives	To compare study emollient types, medium- (16 weeks) and long-term (52 weeks), in respect to: • Patient-reported eczema symptoms • Objective assessment of eczema signs • Quality of life for the child • Impact of eczema on the family • Adverse events • Acceptability of and parent/carer satisfaction with study emollient • Frequency and quantity of study emollient and other emollient use • Use of other eczema treatments (including topical corticosteroids and topical calcineurin inhibitors) • Number of well-controlled weeks Qualitative study: • To understand and optimise recruitment processes • To explore facilitators or barriers to study emollient use • To explore carers' and children's experiences of study emollient use and their views about perceived effectiveness and/or acceptability of study emollients • To contextualise the trial findings, as an aid to interpreting the results and their potential impact on clinical practice
Eligibility criteria	Children aged 6 months or older and less than 12 years; mild, moderate or severe eczema (Patient-Oriented Eczema Measure, POEM, greater than 2, within previous 28 days) diagnosed by an appropriately qualified healthcare professional; no known sensitivity to study emollient; willing to be randomised to and use allocated emollient as sole leave-on emollient for 16 weeks; not participating in another

	study currently or in the last 4 months; carer able to give consent and complete outcome measures.
Randomisation and blinding	1:1:1:1 randomisation ratio; eczema signs (Eczema and Area Severity Index, EASI) at 16 weeks will be assessed by a blinded researcher and the senior trial statistician will be blinded to treatment allocation.
Description of interventions	Study-approved lotion, cream, gel or ointment (with directions to apply twice daily and as required) as the only leave-on emollient for 16 weeks. Other treatments, such as topical corticosteroids, will be used in line with standard care.
Primary outcome	Parent-reported eczema symptoms (POEM) measured weekly for 16 weeks.
Secondary outcome	• Parent-reported eczema symptoms (POEM) measured monthly for 52 weeks) • Eczema signs (EASI, by blinded assessor) at 16 weeks • Parent reported use of study emollient/other eczema treatments measured weekly for 16 weeks • Satisfaction with study emollient at 16 weeks • Adverse effects collected weekly for 16 weeks and then monthly until 52 weeks • Prescriptions of relevant treatments from electronic medical record (EMR) over 52 weeks • Atopic Dermatitis Quality of Life (ADQoL) at 6, 16 and 52 weeks • Child quality of life (Child Health Utility 9D, CHU-9D) at 6, 16 and 52 weeks • Dermatitis Family Impact (DFI) at 16 and 52 weeks Data will also be collected on personal costs, healthcare contacts and prescriptions (by parent-report and review of participant's EMR after 52 weeks); and acceptability of study emollients and study procedures.
Number of participants	520 (130 per group).
Duration of study	Participants: The primary end point of the study is at 16 weeks. Participants will be followed-up for 52 weeks. Trial: Total duration 44 months, including 8 months set-up, 32 months recruitment (with 9 month internal pilot) and follow-up, and 9 months analysis and reporting.
Statistical methods	The sample size was calculated to detect a minimum clinically important difference (MCID) of 3.0 in POEM scores between any two groups with 90% power assuming a standard deviation (SD) of 5.5 and 20% loss to follow-up. To account for multiple testing, we assumed a significance level of 0.0083 (0.05/6 pairwise comparisons equivalent) In an intention-to-treat analysis, we will use linear mixed models to explore weekly POEM scores and determine whether there are differences in mean scores between treatment groups after adjusting for baseline POEM values and all stratification and minimisation variables used in the randomisation. All analyses will be documented in the Statistical Analysis Plan (SAP), which will be finalised

	prior to database lock and un-blinding. This will include methods to deal with missing data and sub-group analyses.
Nested qualitative study	Initial recording of ~10-40 recruitment interviews with rapid analysis and feedback to recruiters to optimise recruitment process; in particular, identifying carer preferences and readiness to use allocated emollient as the only leave-on treatment for the first 16 weeks. Two rounds of interviews with carers +/- children participants, including those who withdraw (actively or passively) and those who change emollients. First round with ~20 participants within first four weeks, with focus on emollient acceptability and perceived effectiveness. Second round with ~40 participants after 16 weeks will focus on experiences of emollient use and decision making around future use. Thematic analysis using constant comparative method.
Keywords	Eczema, RCT, emollients

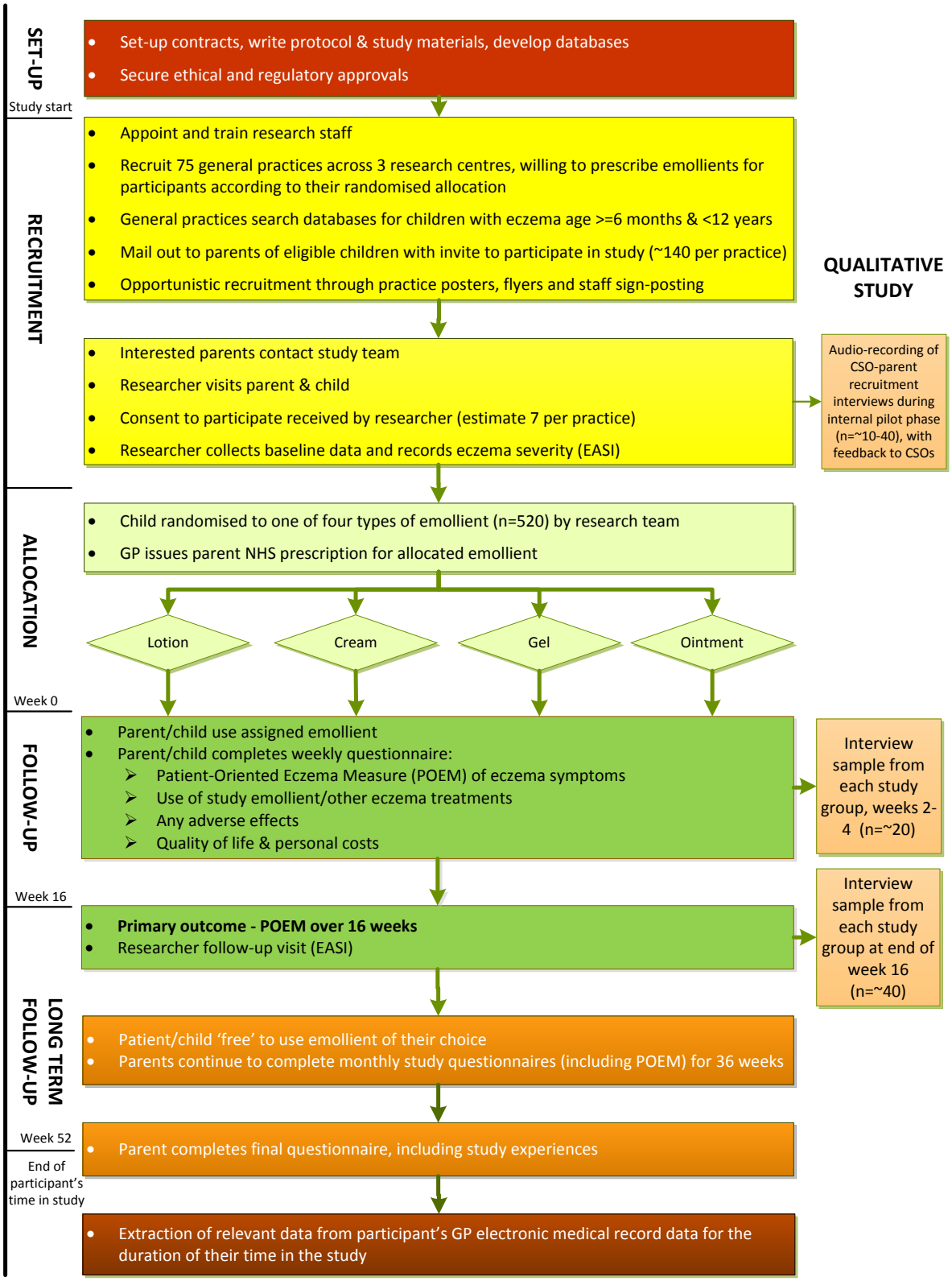
4 Abbreviations

ACBS	Advisory Committee for Borderline Substances
ADQoL	Atopic Dermatitis Quality of Life scale
AE	Adverse Event
AR	Adverse Reaction
BRTC	Bristol Randomised Trials Collaboration
CCG	Clinical Commissioning Group
CEBD	Centre for Evidence Based Dermatology
CI	Chief Investigator
COMET	Choice of Moisturiser in Eczema Treatment
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CSO	Clinical Study Officer
CTA	Clinical Trial Authorisation
CHU-9D	Child Health Utility 9D scale
CTIMP	Clinical Trial of an Investigational Medicinal Product
DFI	Dermatitis Family Impact questionnaire
DSUR	Drug safety Update Report
EASI	Eczema Area and Severity Index
EMR	Electronic Medical Record
EudraCT	European Clinical Trials Database
FP10	Family Practice form 10 (for prescriptions)
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Healthcare professional
HOME	Harmonising Outcome Measures in Eczema
HRA	Health Research Authority
ID	Identification number
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-To-Treat

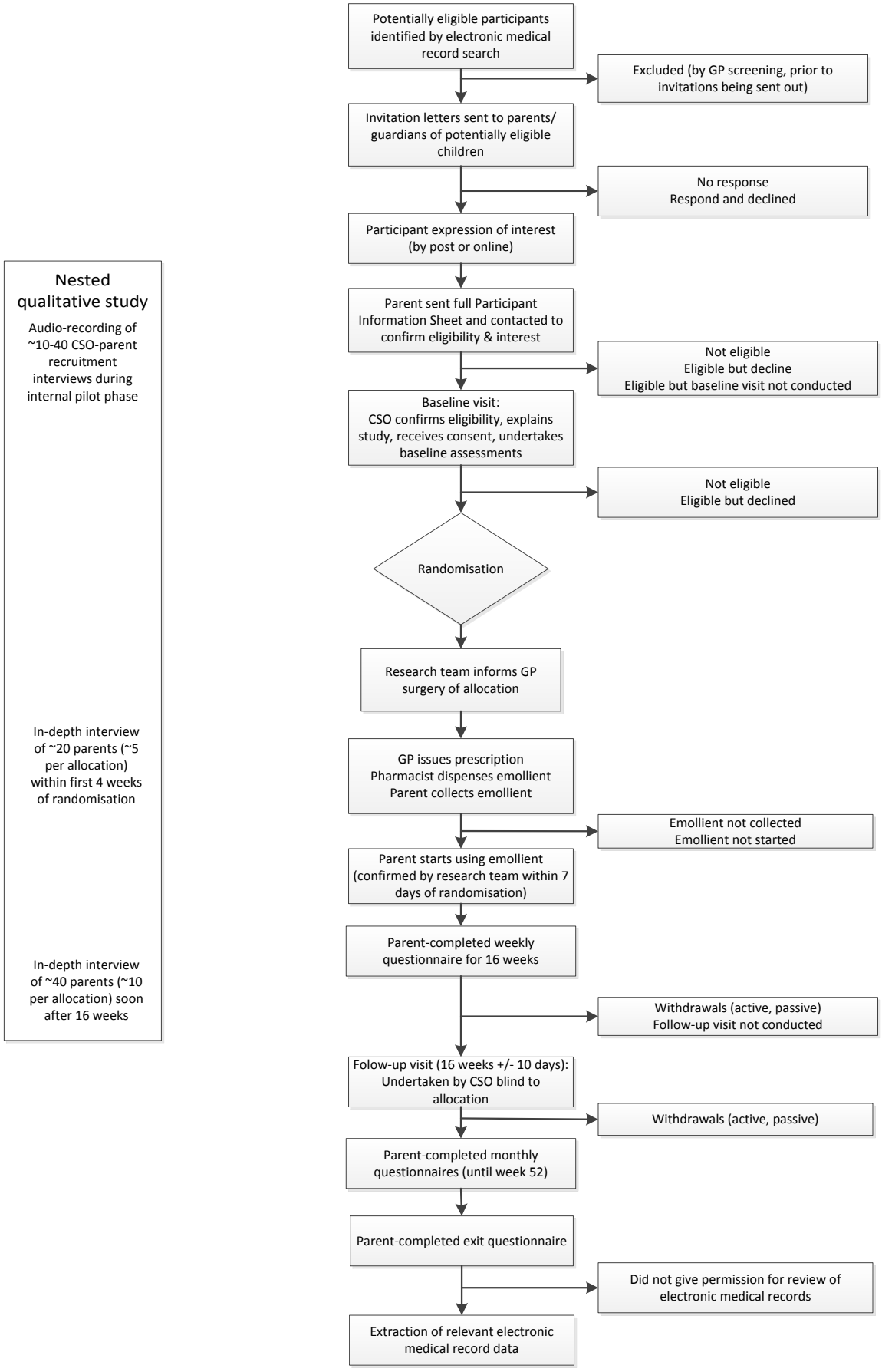
MCID	Minimum Clinically Important Difference
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
PI	Principal Investigator
POEM	Patient-Oriented Eczema Measure
PPI	Patient and Public Involvement
RA	Research Associate
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMS	Short Message Service (text)
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Coordinator
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TM	Trial Manager
TMG	Trial Management Group
TS-/DM-C	Trial Steering/Data Monitoring Committee
UH	University Hospitals (Bristol)
UK DCTN	UK Dermatology Controlled Trials Network
WHO	World Health Organisation

5 Overview of study

5.1 Study flow chart



5.2 Participant flow chart



5.3 Schedule of data collection

		V_0	Participant questionnaires																V_1	Participant questionnaires									EMR
Week	S	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	16	20	24	28	32	36	40	44	48	52	
Eligibility checks	●																												
Demographics (& consent)		●																											
UK diagnostic criteria for atopic dermatitis		●																											
Opinion about study emollients		●																											
POEM	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	
Eczema pain & bother[2]		●				●				●				●				●											
Use of treatments for eczema[1]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	
Adverse events			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	
Consultations (non-EMR)[3]						●				●				●				●		●	●	●	●	●	●	●	●	●	
Personal costs[4]						●				●				●				●		●	●	●	●	●	●	●	●	●	
DFI		●																●										●	
ADQoL		●						●										●										●	
CHU-9D		●						●										●										●	
Satisfaction with study emollient																		●											
Study experiences[5]																												●	
EASI		●																	●										
EMR review[6]																													●
Nested qualitative study																													
Audio-recording of baseline visit		○																											
Round one interviews				←	○	→																							
Round two interviews																			←	○	→								

● = all participants; ○ = sample of participants

S: screening stage (responses to written invitation letters and opportunistic recruits)
V_0 and V_1: research face-to-face baseline & follow-up visits
EMR: Electronic Medical Record

[1] Use of study emollient, other leave-on emollients, and steroids/calcineurin inhibitors for eczema (constructed items)
[2] Two items from the CLOTHES trial
[3] Consultations (non-EMR): health visitor, pharmacist, dermatologist, and dermatology nurse contact from monthly diaries
[4] Personal costs: Out-of-pocket expenses for eczema-related purchases, private/alternative treatments, travel costs to appointments
[5] Reasons stopped using study emollient, adhering to study procedures, beliefs around emollient use
[6] Prescription (study emollients, other emollients, bath emollients, topical corticosteroid/calcineurin inhibitor, wraps, topical or oral antibiotics for infective flares) & consultations (GP & practice nurse/nurse practitioner) data

6 Background

Eczema affects around 20% of children in the UK. In accordance with the recommended nomenclature of the World Allergy Organisation, we use the label "eczema" to refer to the clinical phenotype of atopic eczema/dermatitis.[1] Incidence peaks in the first two years of life and decreases thereafter.[2] It is characterised by dry and inflamed itchy skin, and it can have a significant impact on the quality of a child's life and their family.[3]

The 2010 WHO Global Burden of Disease survey showed eczema ranked first among common skin diseases with respect to disability-adjusted life-years[4] and years lived with a disease.[5] For the child, eczema can adversely influence emotional and social development[6] and may lead to psychological difficulties.[7] Children with eczema appear to be at higher risk of developing attention deficit hyperactivity disorder (ADHD),[8] although there are multiple hypotheses about the biological origin of this association. Parents report loss of sleep and stress, and families can become socially isolated.[9] The resulting impairment in health related quality of life is comparable to that of many other chronic diseases of childhood, including diabetes and asthma.[10] There are no recent figures for the UK but in 1995-96, the total annual UK cost of eczema in children aged 5 years or younger was estimated to be £47M (or £79.59 per child), of which 64% was NHS costs.[11]

The majority of children with eczema have disease of mild or moderate severity and are diagnosed and managed exclusively in primary care.[12] Clinical practice in this group of children is to prescribe a moisturiser (emollient) and topical corticosteroid (TCS)/topical calcineurin inhibitors (TCI) to use alongside to treat or prevent "flares".[13] Applied directly to the skin, emollients reduce water loss by occlusion and/or directly adding water to the dry outer layers of the skin.[14] They may also reduce skin inflammation to some degree, thereby reducing reliance on TCS and TCI. Emollients may also be used to treat symptoms (such as stinging or itching); to act as a barrier for sites such as hands and around the mouth that are open to irritation from saliva, foods and water; and/or used intensively in between flares to prevent flares

However, there are many different emollients available to buy over-the-counter and on prescription and a paucity of evidence that any one emollient is better than another. The main formulations are lotions, creams, gels and ointments, which vary in their consistency from "light" to "heavy". This mainly reflects differences in oil (lipid) to water ratios. Some products also contain humectants which help retain moisture, but emollients containing urea or antimicrobial compounds tend to be reserved for more severe disease.

Currently, when an emollient is prescribed, clinicians and patients may consider the formulation of the emollient in relation to: [14]

- Disease severity – lotions for milder disease, ointments for more severe
- Body site – lighter products for face, heavier products for trunk and limbs
- Cosmetic acceptability of the product – lotions absorb more quickly but may require more frequent application, the effect of ointments may last longer but they stick on clothes and furniture
- Season/climate - light emollients being favour in summers, heavier emollients preferred in winter and
- Container – lotion, creams and gels can all come in pumps, which may be subject to less contamination than open tubs of ointment

Cultural beliefs (e.g. that a heavier emollient is better) may also influence choice and use. However, this is all based on clinical wisdom – evidence on any of these issues in relation to most children with mild/moderate eczema is lacking.

Multiple emollient formularies have been developed by Clinical Commissioning Groups (CCGs) across England to guide clinicians and parents, but they vary widely in their recommendations which reflects the absence of any evidence regarding the comparative clinical and cost-effectiveness of different products. Clinicians are under increasing pressure to prescribe on "cost per g/ml" of emollient alone – which assumes that all products are equally acceptable and effective, and ignores the costs associated with unused emollients and repeated consultations for alternative products if first or subsequent emollients are rejected by the family. NICE recommends patients try different emollients in the clinic before choosing.[13] This approach is not practical in primary care, and even in specialist settings the range of emollients available to try can be arbitrary and restricted local formularies and the influence of pharmaceutical companies. Therefore, unless parents have prior personal experience of emollients, most patients consulting in primary care are unaware of differences between emollients; and many primary care clinicians will be unable to advise on grounds other than consistency (from thin and watery to thick and "gloopy") or simple unit cost.

The resulting uncertainty about what to use is detrimental to both families and the NHS. Data from our feasibility study[15 16] and PPI survey[17] for this trial show that families have often tried many different emollients. The current situation where healthcare professionals (HCPs) recommend different emollients and carers find an effective emollient through a process of "trial and error"[18] is frustrating for families,[19] can take considerable time and some families may "give up" using emollients altogether, leading to sub-optimal eczema care or use of unorthodox treatments which may be harmful.[20]

This is an issue of importance to both patients and healthcare professionals. In the recent (2013) James Lind Alliance research priority setting partnership for eczema, "Which emollients are the most effective and safe in treating eczema?" emerged as one of the highest ranked uncertainties requiring further research.[21] In 2007, NICE recommended research to identify "the most effective and cost-effective combinations of emollient products to use for the treatment of childhood atopic eczema".[13] A recently published Cochrane review identified 77 trials, comprising 6603 participants, evaluating the effectiveness of emollients.[22] The majority (70/77) were at 'unclear' to 'high' risk of bias, and very few studies compared similar interventions. Only 13 studies assessed participant satisfaction with treatment and the reporting of adverse events, although included in over half of the studies (41/77), was limited. The authors were unable to conclude whether some of the moisturisers, or their ingredients, are better than others, as most head-to-head comparisons had been evaluated in single studies, which generally had small sample sizes.

7 Rationale

Research comparing the clinical effectiveness and acceptability of commonly used different emollients is needed to provide evidence upon which clinicians and carers/patients can decide which emollient to try first. Smarter prescribing will help prescribers and carers gain "control" over the eczema more quickly, reduce frustration and inconvenience for families, and potentially produce cost savings to the NHS through cost-effective prescribing and fewer repeat consultations to change emollients.

Some emollients are decades old and it has not been in the interest of pharmaceutical companies to put their products in a head-to-head comparison with others in a clinical trial. We, therefore, want to independently evaluate in a pragmatic trial with a validated, patient-reported outcome the effectiveness of the four types of emollients commonly prescribed for children with eczema. Our aim is not to reduce choice, but to reduce uncertainty and the consequences of "trial and error" prescribing.

7.1 Research question

Our research question is: "Which is the best type of emollient to prescribe for treating the symptoms of childhood eczema – a lotion, cream, gel or ointment?"

- Eczema symptoms will be measured using the Patient-Orientated Eczema Measure (POEM), with the primary outcome being weekly POEM scores for 16 weeks.
- The qualitative sub-study will allow us to contextualise and aid interpretation of effectiveness findings in relation to acceptability and implications for clinical practice.

7.2 Justification of research question and study emollients

Research comparing emollients for eczema is challenging because of the many possible research questions and emollients. Clinicians in the NHS can prescribe over 70 different proprietary and non-proprietary emollients, which are variously designated as cosmetic products, medicines and medical devices. There is no agreed upon classification system, but formularies and guidelines commonly group them by formulation (lotion, cream, gel and ointment).

The BEE study seeks to provide evidence around the effectiveness and acceptability of first-line emollients as a leave-on treatment, so for this reason we will only compare paraffin-based emollients (which are the majority) and have excluded second-line products that contain antimicrobials or urea. By comparing emollients across the four main types of lotion, cream, gel and ointment, we will provide evidence to inform current prescribing practice for most children with eczema who are diagnosed and treated in primary care, whose disease is mainly mild/moderate in severity. It also seeks to answer the question of greatest importance to carers of children with eczema who completed our PPI survey: "Which is the best emollient for treating the symptoms of childhood eczema – lotion, cream, gel or ointment?"

7.3 Choice of primary outcome, bias and blinding

We favour a patient-reported primary outcome because the symptoms of eczema are much more important to families of children with eczema than objective measures which are based on skin appearance.[24] We have asked PPI members about the influence of brand and packaging on use and perceived effectiveness of different products. In common with participants in the feasibility trial (COMET) and respondents to our public survey when preparing the current funding application, PPI group members and their children had used many different emollients. While some disliked the "medicalised" nature of the emollients and may initially value products that look more attractive and "cosmetic", they also told us that the proof was in its use – that is, whether it helped with eczema

symptoms and didn't cause any adverse reactions. Despite this, we acknowledge that not all participants in the trial may feel the same and performance bias is usually subconscious.

It is not possible to blind clinicians/parents and researchers to the emollient being used in a trial comparing the four different formulations of lotion, cream, gel and ointment because: only the lotion, cream and gel products could, in theory, be repackaged into plain pumps (the ointment would still have to come in a tub) with attendant risk that one or more of the emollients may not be dispensed as well from a universal pump compared to the original device, thus potentially influencing use of and satisfaction with the product; "over-packaging" may be more feasible, but PPI members were concerned about the effects on the usability and portability of the emollients; and trying to obtain "unlabelled" emollients directly from the manufacturers would be fraught with logistical and commercial barriers.

Having the GP prescribe and the patient's pharmacy issue the randomly allocated study emollient by the normal route maintains the pragmatic nature of the trial and does not undermine collection of data pertinent to a later economic evaluation. That is, if participants were given their complete masked supply of emollients at randomisation by the study team, rather than via their local GP and pharmacy, dispensing costs would not be included; the amount used may be affected; and parent's consulting behaviour might change. Consultations were shown in the feasibility study to be the main driver for costs to the NHS in the care of these children.[16]

We will minimise the potential for performance bias by ensuring that, at the point of consent, parents are willing to use any of the four types of emollient for the first 16 weeks. We will also measure parent opinions regarding the four different types of study emollient at baseline, and explore whether reported effectiveness is linked to high/low prior expectations of effectiveness in a sub-group analysis. The collection of an objective measure of eczema severity (EASI) by a masked researcher as a secondary outcome allows us to examine outcomes in relation to signs of eczema.

8 Aims and objectives

8.1 Aim

The aim of the study is to compare the effectiveness and acceptability of four different types of emollient commonly used to treat eczema.

8.2 Objectives

The key objectives are to compare types of study emollients, medium (16 weeks) and long-term (52 weeks), in respect of:

- Parent-reported eczema symptoms
- Objective assessment of eczema signs
- Quality of life for the child
- Impact of eczema on the family
- Adverse effects
- Acceptability of and parent satisfaction with study emollient
- Frequency and quantity of study emollient and other emollient use
- Use of other eczema treatments (including TCS and TCI)
- Number of well-controlled weeks

The specific objectives of the qualitative study are:

- To understand and optimise recruitment processes
- To explore facilitators or barriers to use and follow up with participants who stop treatment early
- To explore carers' and children's experiences of study emollient use and their views about perceived effectiveness and/or acceptability of study emollients
- To contextualise the trial findings, as an aid to interpreting the results and their potential impact on clinical practice.

9 Trial design

9.1 Study design

Pragmatic, multi-centre, individually randomised, parallel group superiority trial of four types of emollient in children with eczema, with internal pilot and nested qualitative study. The recruitment target is 520 children (130 in each arm), with an internal pilot RCT during the first nine months of recruitment in all three centres to monitor and respond to any issues with recruitment (target of 180 participants by 9 months of recruitment from ~25 practices).

9.2 Setting

Primary care (GP practices) in and around Bristol, Southampton and Nottingham (n=~75, or approximately 25 from each centre).

Most children with eczema are diagnosed and treated exclusively in primary care. The GP prescribes the study emollient and retains clinical responsibility for the participant – usual care is otherwise not affected. The study emollient is dispensed by the carer's pharmacist as normal.

9.3 Population

Children with eczema.

9.3.1 Inclusion criteria

Children must:

- be aged between 6 months and less than 12 years of age
- have eczema diagnosed by an appropriately qualified healthcare professional (registered doctor, nurse or health visitor)
- mild eczema or worse (POEM score>2 within previous 28 days)

The person giving consent must:

- have parental responsibility for the participant
- be willing to use the randomly allocated emollient type as the only leave-on emollient for 16 weeks.

9.3.2 Exclusion criteria

Child:

- known sensitivity to study emollients or their constituents
- participating in another research study currently or in the last four months
- any other known adverse medical or social circumstance that would make invitation to the study inappropriate (as determined by GP practice staff)

The person giving consent:

- unable to give informed consent
- insufficient written English to complete outcome measures

9.4 Interventions

Participants will be randomised to one of four types of emollient:

1. Lotion
2. Cream
3. Gel
4. Ointment

These four types of emollients are among the most commonly prescribed for childhood eczema, but they are also available to buy over-the-counter (not prescription-only items). Emollients are the foundation of treatment for all children with eczema and it would be considered unethical to include a "no emollient" group. All participants will, therefore, be advised to use an emollient and there is no "control" or "placebo" group.

Parent/carers will be asked to agree to use their study emollient as the only leave-on emollient for 16 weeks. GPs will be asked to prescribe them with directions to apply twice daily and when required, as per common clinical practice. The amount of emollient prescribed during the study, by repeat prescriptions, will be determined by the family. Clinicians will be free to issue prescription for a smaller amount (e.g. 125g), if requested (e.g. for travel purposes). All study emollients can also be used as soap substitutes, and parents will be encouraged to use their allocated emollient for this purpose too. However, use of other emollients as wash products will be permissible and not be classed as contamination (see 9.4.1 Definitions of adherence and contamination).

If the family or their doctor/nurse judges that continuing their study emollient will be detrimental or the parent/child decides that they simply don't like it, they can stop using their allocated emollient and seek an alternative from their GP. In this instance, the GP/family will be encouraged to use another emollient that is of the same type. This will not affect their participation in the trial, and so they will continue to be followed up, unless they choose to withdraw at this or any other time.

Clinical management of eczema will otherwise be as usual – with treating clinicians and participants free to make clinic appointments, referrals and to continue to use or change other treatments (including topical corticosteroids) as normal.

9.4.1 Definitions of adherence and contamination

To assess adherence to the allocated medication, for each patient, we will count the number of days of self-reported use of the allocated type of emollient and express that as a proportion of the number of days for which non-missing emollient data are available. Contamination will be assessed by calculating the proportion of days (among days where non-missing emollient data are available) where a non-allocated emollient type was used.

9.5 Outcomes

A complete schedule of data collection can be found in the table presented within the 'Schedule of data collection' section. For ease, a brief overview is provided below.

In accordance with the recommendations of HOME (Harmonising Outcome Measures in Eczema, www.homeforeczema.org), data will be collected in the four key domains of symptoms, clinical signs, long-term control and quality of life. POEM and EASI are the core outcome instruments recommended by HOME for measuring patient-reported symptoms and clinical signs, respectively.[25] The primary outcome is weekly Patient-Oriented Eczema Measure (POEM) for 16 weeks. Thereafter, POEM will be collected monthly until 12 months. We are following-up patients for one year because eczema is a relapsing-remitting condition where symptoms can be seasonal and there is paucity of long-term outcome data in relation to emollient use in children with eczema.

9.5.1 Primary outcome

The primary outcome is parent-reported eczema symptoms (POEM, measured weekly for 16 weeks).

POEM is a patient-reported outcome that can be completed by proxy (carer report) and captures symptoms of importance to parents and patients over the previous week.[24] It demonstrates good validity, repeatability and responsiveness to change,[26 27] and was favoured as the main outcome by

PPI. We have chosen repeated measures because eczema is a relapsing and remitting long-term condition and this approach captures effectiveness of treatments better than comparing outcomes at a single time point.

9.5.2 Secondary outcomes

The following secondary outcomes (time period) will be collected:

- Parent-reported eczema symptoms (POEM, measured monthly for 52 weeks)
- Eczema Area Severity Index (EASI) (assessment of eczema signs, by blinded assessor at 16 weeks)
- Use of study emollient/other eczema treatments (daily use reported weekly for 16 weeks, then monthly until 52 weeks)
- Parent-reported satisfaction with study emollient (at 16 weeks)
- Adverse events (localised reactions – such as itching, burning, redness/inflammation, pain, skin infections – and slips and falls, weekly for 16 weeks, then monthly until 52 weeks)

Child- and family-oriented quality of life measures will be collected at baseline, weeks 6, 16 and 52 by means of participant questionnaires:

- Disease-specific – child ADQoL;[28] family – Dermatitis Family Impact questionnaire (DFI)[29]
- Generic – child CHU-9D[30 31] (currently validated for children aged 7 and over, with pilot versions for those aged 5-7 and additional guidance notes and validation questions for those under 5)

An exit questionnaire about trial participation will be administered at 52 weeks.

With a view to carrying out economic analyses in the future, we will also collect data on personal costs related to eczema, healthcare consultations and prescription data. A separate health economic analysis plan will be developed.

9.6 Duration of study

The total duration of the study is 44 months. This includes:

- Set-up: 8 months
- Recruitment: 20 months
- Primary outcome follow-up period: 20 months
- Electronic Medical Record (EMR) review: 20 months
- Data cleaning, analysis and reporting: 13 months

The timelines will be monitored throughout the trial, reviewed by the trial committees, and adjusted as necessary to reflect the progress of the trial.

10 Trial procedures

10.1 Selection and training of recruiting sites

Practices will be recruited via NIHR Clinical Research Networks (CRNs). As part of this process, we will ensure that CCGs and GP surgeries are willing to prescribe emollients for participants according to their randomised allocation.

Participating practices will be given training by the Trial Manager (TM)/Clinical Study Officer (CSO) at an initiation visit, which will take place before they approach any patients. First, they will be given verbal and written instructions of how to run the participant search, screen the results and then send written invitation to potential participants. Practices will be reminded to ask GPs to provide a reason for any participants that they exclude from the study, as this information will be collected by the research team. Next, arrangements for initial and on-going prescription of allocated emollients to participants will be agreed. Posters and flyers will be provided to the practice, so that they might opportunistically sign-post potential participants to the research team. Practice staff will not directly recruit participants to the trial by any other means.

10.2 Recruitment of participants

The stages of participant recruitment are shown in the Participant flow chart (5.2 Participant flow chart). We will identify children with eczema (mild, moderate and severe) via an electronic query-based records search run by practice staff at the GP surgeries. The record search, developed by the research team, will identify children between 6 months and less than 12 years of age, with an eczema diagnosis (Read code) in their records, and prescription of a relevant eczema treatment in the previous 12 months. The GP or a delegated member of the practice team will screen the search results for inclusion/exclusion criteria and any other known adverse medical or social circumstance that would make invitation to the study inappropriate. If the search identifies multiple siblings who are potentially eligible, GP practice staff will be instructed to exclude the older sibling(s) as a rule prior to invitation to the study. The rationale is that eczema is more common in younger children (and so the eczema is more likely to be currently active), and the parent may be less likely to have established a preference for a particular emollient. Surgeries will be asked to provide the research team with the number of participants excluded by the GPs, along with a brief reason for exclusion. Parents of the remaining potentially eligible children will be sent an invitation pack, comprising an invitation letter, study flyer and response slip.

In addition, we will also recruit participants opportunistically, by placing a study poster in the waiting room of each participating GP surgery. Contact details for the local research team will be included on the poster, but we will also supply the surgery with flyers to hand out to interested parents.

Based on our feasibility trial (COMET) findings, we expect the average practice to identify 160 potentially eligible children from their record searches, of whom we expect 20 will be excluded by the practice. Of 140 invitation letters sent, we expect replies will be received from 25 parents, of whom 10 children will be potentially eligible, which we expect will lead to 7 of those children being randomised. Therefore, we will need ~75 practices (~25 per centre) to achieve our target sample size of 520 participants within the 20-month recruitment period.

10.3 Confirmation of eligibility and consent

Interested families will be asked to complete an expression of interest form along with a brief screening questionnaire (POEM) that the research team will use to confirm eligibility. Ineligible participants (POEM score indicates clear/no eczema) will be notified.

Eligible participants with POEM scores indicating mild eczema or worse (>2) will then be contacted by a local researcher to explain more about the study and schedule a baseline assessment at a time and location convenient to the participant. Ahead of the visit, the parent/carer will be sent a more detailed participant information leaflet to read. At the baseline visit, CSOs based in each centre will: explain about the study in more detail; confirm understanding of the randomisation process and willingness to use one of the four types of randomly allocated study emollients for 16 weeks; receive consent; and collect baseline data (see 11.3). If it has been greater than 28 days since the parent completed the POEM confirming eligibility, this will be repeated, and only children with a POEM >2 within the last 28 days will be recruited to the study.

Informed consent will be received from the child's parent/legal guardian prior to any procedures that are specifically for the purposes of the trial and are outside routine care. For children approximately 7 years and older, the option of providing assent will be offered alongside parental consent. The right of a participant to refuse participation without giving reasons will be respected. Similarly, it will be made clear that participants are free to withdraw at any time from the trial without giving reasons and without prejudicing his/her future treatment (see 10.5.2).

As part of the invitation screening process, eligibility to take part in the trial will be confirmed by the participant's GP, prior to randomisation. Written consent will be taken by an appropriately trained CSO.

10.4 Allocation

Participants will be randomised by the TM using a validated web-based randomisation system supplied by the Bristol Randomised Trials Collaboration (BRTC), using computerised randomly-generated numbers. The system is available 24 hours a day with minimal downtime. System data are backed up daily.

Randomisation will be performed using secure allocation concealment that cannot be changed once allocated. Participants will be randomised in a 1:1:1:1 ratio to the four groups, stratified by centre and minimised by baseline POEM (mild versus moderate/severe) and participant age (less than 2 years old versus 2 years and above).

The TM will notify the appropriate GP surgery of the participant's allocation. The GP will then issue the initial prescription and make it available for repeat prescription. Parents of participants will be contacted by the research team within one week of randomisation to ensure that they have obtained and started using the study emollient. If the parent has not picked up the prescription at this time, the research team will encourage them to do so as soon as possible and will telephone them again a few days later to check that this has since been picked up. The date the prescription was picked up and its application started will be recorded by the research team.

10.5 Follow-up of participants

10.5.1 Duration of participant involvement

From the point of randomisation, participants will take part in the trial for 52 weeks, with the primary outcome collected over the first 16 weeks. Participation in the trial concludes after the final 52-week questionnaire is completed online or returned to the local researcher by post.

10.5.2 Withdrawal from the study

Parents or their clinicians will be free to withdraw the participant at any time, without any consequences for their usual care or follow-up. Withdrawal from the study will be classed as "active" (the participant/clinician contacts the research team saying that they no longer want or are unable to take part) or "passive" (participants stop completing study questionnaires, fail to attend

the 16 week appointment and/or do not respond to communications from the research team). We will analyse any data already collected/undertake the EMR review, unless the participant expressly wishes for associated data not to be included prior to the database being locked.

Participants who actively withdraw will be asked to provide a brief reason for why they would like to withdraw and some will be invited for an interview as part of the qualitative study (see section 12, Qualitative study).

10.6 Blinding

For reasons discussed earlier (see section 7, Rationale), the treatments themselves will not be re-packaged or in any way altered, and they will be prescribed through normal routes. The table below summarises who will be blinded to treatment allocation:

Table 1: Blinding to treatment allocation

Individual(s)	Status	Notes
Participants (children and carers)	Not blind	It is not possible to blind participants or treating clinicians to allocation.
Treating clinicians	Not blind	
BRTC database staff, Trial Coordinator (TC), trial administrator and qualitative RA	Not blind	BRTC staff will maintain the randomisation database. The trial coordinator/administrator will randomise participants/notify clinicians; check with the parent that the correct allocated emollient has been obtained and started by 7 days post-randomisation; and be the initial point of contact for all enquiries relating to issues with the emollients. The qualitative RA will undertake interviews where the type/name of study emollient will be discussed.
Junior statistician	Partially blinded†	The administrator will enter the data from ~100 (~20%) participants completing paper questionnaires which emollient a participant reported using, but will not know allocation for certain. Will know which of four groups individual participants have been allocated, but will not know which group corresponds to which type of emollient. They will be therefore able to prepare the reports for the TS/DM-C for both open (aggregated data) and closed (disaggregated data) sessions.
Dr Heawood and Dr Banks (supervising Qualitative RA)	Partially blinded‡	The RA, Dr Heawood and Dr Banks will select participants for interviews based on allocation/use and during the interviews the RA will specifically ask about the different emollient types. The ~60 transcripts will contain direct (i.e. name) and indirect

		references (e.g. consistency) to the emollient(s) being used/discussed. However, Dr Heawood/Banks will not know the allocation of the other ~460 participants.
TM and CI	Almost blind‡	For the small number of anticipated SAEs (~1%, ~5 participants) the TM and CI will need to know which emollient the child was using, which may not be the allocated emollient
Other TMG members*	Blinded	Procedures will be put in place (see below) to maintain blinding both within and outside of project meetings.
CSOs	Blinded	Blinding will be monitored by means of self-report.

† will know the group allocations by not name of study emollient
‡ will know name of emollients for some participants
* Dr MacNeill (senior statistician), Dr Santer & Prof Thomas (PIs), Ms Barrett (pharmacist), Dr Lane & Dr Taylor (BRTC), Prof Hay & Prof Williams (senior researchers), Dr Baxter (knowledge mobilisation), Mrs Roberts & Ms Jameson (PPI&E)

The CSOs and the senior trial statistician will be blinded to participants' allocation until analyses are complete. This is to ensure that the CSO and the statisticians are unbiased respectively in their assessments of eczema severity and in the analysis and interpretation of the trial data, i.e. they are not influenced by knowledge of the type of emollient being used. The parents and clinicians involved in the care of participants will not be blinded and will know which treatment they have been advised to use.

Procedures to maintain blinding to allocation will be written and followed. First, neither party will have access to the randomisation system, and so will not be able to identify which emollient type has been assigned to which participant by this means. Second, a "Chinese wall" (an information barrier to prevent exchanges or communication that could lead to unblinding) will be established between the unblinded and blinded members of the research team. Third, clinicians and parents will be asked not to disclose which treatment they are using to the CSO. Fourth, prior to the 16 week follow-up visit, parents will be asked to make sure that the emollient container is hidden from view; and in order to minimise the risk of un-blinding due to visible or tactile differences between emollients when applied to the skin, asked to maximise the amount of time between application and the assessment.

CSO blinding will be assessed using the Bang's blinding index,[32] which takes a value between -1 and +1: +1 indicates complete lack of blinding, 0 is consistent with perfect blinding and −1 indicates opposite guessing, which may be related to un-blinding. The index will be presented with confidence intervals.

Because the parents of children in the trial and all treating clinicians will know the treatment allocation, un-blinding procedures are not required.

10.7 Stopping rules and discontinuation

Recruitment, retention and adherence will be monitored monthly by the TMG. If progress is below target, strategies will be implemented to remedy this as agreed by the Trial Steering/Data Monitoring Committee (TS/DM-C) and/or the NIHR HTA.

An internal pilot RCT will be conducted across all three centres over the first nine months of recruitment. Progression criteria based on recruitment/retention rates, adherence and contamination (as stated in the table below) will be assessed by TS/DM-C at nine months:

Table 2: Internal pilot progression criteria

Criteria to be assessed at 9 months	Proposed action
>=80% of target recruitment and retention (180 participants); adherence>80% and contamination <20%	Continue with main trial as planned
70 – 79% of target recruitment or retention; adherence 70-79% or contamination 20-30%	TS/DM-C discuss problems with the Trial Management Group and urgently implement remedies
< 70% of target recruitment or retention; adherence <70% or contamination >30%	Discuss plans with TSC/DM-C and NIHR HTA. Consider stopping trial.

10.8 Participant stipends and payments

Participating families will receive no monetary payment for taking part in this trial. However, in recognition of participant's time and to encourage retention in the study/data collection, participants will be offered two £10 vouchers at the baseline and around the 16-week visits. We may also offer the child a small gift, e.g. "bee" toy of about £5 in value.

10.9 End of trial

The end of the trial will be the last data collection item of the last subject, defined as 52 weeks after randomisation of the last participant.

11 Data collection

A complete schedule of data collection can be found in the table presented in section 5.3, and is also depicted in the "5.2 Participant flow chart". Data will be collected by means of researcher visits, parent-completed questionnaires and EMR review.

11.1 Participant screening assessment

Potential participants will be sent a recruitment pack containing information about the study, a reply form & short questionnaire. Those interested in taking part in the study will complete the short screening questionnaire containing the POEM. These responses will be recorded on the study database. Respondents who meet initial automated eligibility checks (e.g. POEM score >2, indicating mild or worse eczema) will then be contacted to confirm eligibility and arrange a baseline visit with the child and their parent at a time and location convenient to them, which is likely to be at the participant's home.

11.2 Decline form

Potential participants who are not interested in taking part in this study will be asked to provide their reasons for declining on a study invitation reply slip. The form will ask respondents to indicate the reason(s) they are declining taking part (e.g. too busy, eczema is currently clear, not interested in the study, etc.). This information will be useful in designing future trials and may provide information about barriers to recruitment, should we encounter difficulties reaching our pilot phase recruitment target.

11.3 Participant baseline assessment

During the baseline visit, the CSO will receive consent (see section 10.3), administer baseline questionnaires and conduct the physical assessment of eczema severity (EASI). If it has been greater than 28 days since the parent completed the screening POEM, this will be repeated to confirm eligibility. Baseline questionnaires will include: socio-demographics, UK Diagnostic criteria for atopic dermatitis,[32] parent opinion about study emollients, past/current treatments for eczema, POEM and quality of life measures (DFI, ADQoL, CHU-9D). They will go through the patient diary and answer any questions related to this or the study in general.

11.4 Participant follow-up assessments

Regarding follow-up questionnaires and the 16-week visit, participants will be offered electronic reminders. Participants who opt to complete questionnaires on paper will receive SMS and telephone reminders, while those who choose to complete these online will receive email and telephone reminders. For those parents who are struggling to complete the questionnaires or for those questionnaires returned with missing data, an option to complete these over the telephone will be offered.

11.4.1 Weekly parent-completed questionnaire

Families will be given the option of online or paper questionnaires (weekly for the first 16 weeks, then monthly until 52 weeks). Weekly questionnaires will include: POEM; use of eczema treatments; and adverse events. Monthly questionnaires will additionally include: consultations for eczema with health visitors, pharmacists and dermatology specialists; personal costs; and eczema pain and bother questions (at weeks 4, 8, 12, and 16 only).

11.4.2 Other questionnaires

At 6, 16 and 52 weeks, two eczema-specific quality of life questionnaires (ADQoL, CHU-9D) will be included after the usual weekly questions. Parents will be asked to complete an emollient satisfaction questionnaire at 16 weeks, plus a final exit questionnaire about overall study experience.

11.4.3 Researcher follow-up visit

A CSO will meet with the parent and child at 16 weeks (+/- 10 days). Still blind to allocation, they will administer EASI.

11.5 Electronic medical record (EMR) review

After 52 weeks of participation, the participant's primary care electronic medical record will be reviewed for data (from 4 weeks before until 52 weeks after date of randomisation) on:

- Prescriptions: number, type and quantity of leave-on and bath emollient(s), topical and oral corticosteroids, topical calcineurin inhibitors, topical and oral antibiotics, and bandages
- Eczema-related consultations (GP, nurse), referrals, out-patient appointments and prescriptions will be collected from the EMR at 12 months.

12 Qualitative study

12.1 Background and aims

The value of qualitative research in RCTs is established,[33] but it is particularly useful in the evaluation of healthcare interventions such as emollient use, where regular long-term use involves social or behavioural processes. The aims of this nested study are:

1. To support and optimise recruitment processes (in particular, maximise recruitment/retention, and minimise contamination, cross-over and drop out)
2. To complement, explain and aid understanding of the quantitative findings regarding the delivery/receipt of the intervention, its acceptability and perceived or experienced benefits or harms.

Specifically, with respect to the first aim, we will identify how the content and/or style of the baseline appointment, when the study is explained and consent received, appears to influence participant willingness to both consent to taking part and adhere to using the study emollient as the only leave-on moisturiser. Information on how different interactions appear to influence these outcomes will be fed back to the CSOs undertaking these visits and their effects monitored.

Regarding the second aim, we will use qualitative data to help explain quantitative findings around effectiveness. We will look at the perceived effectiveness and acceptability in each emollient group and compare it with the quantitative data to establish whether and why there may be any differences between them. The qualitative data will improve our understanding of effectiveness (or lack of) by giving detailed accounts of how emollients were applied. Such an understanding might help inform clinical guidelines and give a more complete picture of the impact of emollients on a child's skin and on several aspects that are related to its use. Furthermore, data from those who stopped treatment early in all trial arms will give valuable insight into barriers to use and possibly strategies for overcoming these in future patients.

12.2 Methods and setting

Data will be collected from trial participants by means of audio-recording the baseline visit (in person) or by interviews with a qualitative research associate (face-to-face, either in a setting of participants' choosing (usually their homes) or, where this is not possible, over the telephone). For the interviews, semi-structured topic guides will be employed, which focus on trial-related issues (e.g. prior experiences and beliefs about emollient use, trial processes and procedures, etc.) and existing research literature.

We will also aim to include older children in the interviews. We recognise that paired interviews can influence responses from either respondent,[34] but feel that this is outweighed by the value of collecting data directly from the children for whom the study emollient has been prescribed. Interactions will be captured using an encrypted digital voice recorder, transcribed and anonymised to protect confidentiality.

12.3 Sampling

During the nine-month internal pilot, we will audio-record a sample of ~10-40 baseline visits, when the study is explained and consent is received. These visits will be primarily sampled by recruiting centre and CSO. However, as the study progresses, we may sample by parental characteristics if early recordings suggest that important variations exist that effect the style, content and outcome of the encounter.

We will then recruit two cross-sectional samples from each trial group at two-time points. The first will be with participants during their first four weeks in the study (i.e. post-randomisation). We will include up to five participants from each group in this part of the study (total=~20) and we will purposively sample by: eczema severity and frequency or type of emollient use/co-use (as assessed by participant questionnaires), and will include those who have stopped using the allocated treatment.

The second sample will be interviewed soon after the primary outcome period at 16 weeks. Participants will be recruited from each trial group and will be sampled by age, eczema severity, gender, location (indicator of socioeconomic status) and ethnicity. Some participants from the first round of interviews may also be invited to participate in the second round. We expect to achieve data saturation by recruiting 10 participants in each trial group (total=~40).

12.4 Recruitment and consent

For the baseline audio-recordings, parents will first be asked to give verbal consent for this aspect of the study prior to the CSO initiating the baseline visit proper. After the completing the baseline visit, parents will be asked to confirm their continued consent in writing.

For the two cross-sectional interviews that occur post-randomisation, parents/carers will be asked to indicate on the trial consent form whether they are willing to be approached by a member of the research team at a later stage to take part in this aspect of the study. We will record this information in the study database. We will contact those parents who agreed (and meet our sampling requirements) at the above described time points with an invitation letter and additional qualitative study participant information sheet. A qualitative researcher will follow up the postal invitations with a telephone call approximately a week later to establish whether the parent is interested in taking part in the interview.

At the discretion of parents/carers, children with eczema (probably from around 7 years of age) who are present at face-to-face interviews will be invited to take part, so that it becomes a three-way conversation. Written assent will be sought from participating children.

12.5 Data collection

The CSOs will audio-record their own baseline visits, which will be conducted as per their training, i.e. “as normal”. Baseline visits will normally take 20-30 minutes and will not be changed or significantly prolonged by the audio-recording.

Interviews will be done by a qualitative researcher and are expected to last between 45-60 minutes. Topic guides will be used as the basis for the discussion, but with flexibility to allow unanticipated issues to emerge and be further explored in later interviews. We will employ a sub-topic guide for children to encourage their participation where they are interested in doing so.

The first round of interviews will be focused on participants’ use of their assigned emollients and the degree to which it is consistent or different from recommended use. As part of this sample, we will include participants who stop using the emollient early and focus on the barriers to use. Interviewing then will mean that data on the practicalities of emollient application will not be subject to the same degree of recall bias as interviewing after the trial has finished.

As detailed above, the second set of interviews will take place after the 16-week primary outcome has been collected. This will allow participants' overall reflections on emollient use over the full trial period to be compared and integrated with the main trial data from the same period. These interviews will be informed by the themes identified in the first round of interviews. The focus of

these interviews will be on the overall experience of using the assigned emollient, perceived effectiveness and planned future use of emollients.

12.6 Analysis

Analysis will be led by a qualitative researcher, with support from relevant members of the TMG.

Data from the baseline visits will be extracted using a structured template and key aspects of the encounter (structure, process or content) that appear to relate to patient preferences will be transcribed. Data will be examined to ensure that the recruiting researchers are effectively explaining the commitment involved in taking part in the trial, exploring the issue of patient preference and their willingness to use the allocated emollient as intended. The research team will reflect on these data and any strengths or weaknesses identified. Any suggested modified approaches (e.g. ordering of information, key phrases or areas for potential misunderstanding) will be fed back to the CSOs undertaking these visits and incorporated into the baseline standard operating procedure (SOP). The effect of this feedback will be monitored in subsequent recordings and further changes will be made if deemed necessary, in an iterative manner.

Cross-sectional interviews will be recorded and transcribed verbatim. Transcripts will be coded for key categories and concepts, applying the constant comparative method.[35] Data will be compared across groups and within groups. Themes will be identified and refined through continual comparison of data elements with each other in an iterative manner. We will compare user's perceptions and explanations within groups to assess consistency of experience, and across groups to assess how the emollients compare in terms of acceptability and perceived effectiveness. We will also look at participants' comparison with other emollients that they may have used (most participants will have prior experience of other emollients).

13 Study emollients

13.1 Description

The emollient types used in the trial are lotion, cream, gel and ointment. The emollients most commonly prescribed for childhood eczema are classed in to one of these groups by their manufacturers. They are available to buy over-the-counter, i.e. they are not prescription-only items.

Technically, some of these emollients are classed as cosmetic products, some are licensed as medicines, and some are licensed as a medical device. The difference in licenses between the products (cosmetic product, licensed medicine, licensed medical device) does not affect the use of the products by patients and clinicians.

13.2 Manufacture and product characteristics

GP prescribing of specific emollients of each type is restricted by local formularies which vary widely and may change. Therefore, participants will be randomised to a type (lotion, cream, gel or ointment) rather than specific named emollient. However, to reduce heterogeneity within each type of emollients, GPs will be asked to only prescribe emollients which share certain characteristics. Study emollients will therefore be distinct between types (formulation, defined according to manufacturer labelling) and similar within each type (rules for inclusion/exclusion). Further details are provided in Table 3 below.

Table 3: Rules for exclusion/inclusion of different types of emollients

Type of emollient		**Lotion**	**Cream**	**Gel**	**Ointment**
Rules/group shared characteristics	Exclusion	Antimicrobials or urea			
	Inclusion	Paraffin-based			
		Glycerol containing only	No humectant or lanolin	Does not contain povidine	No additives
Example formulary emollients from each group†		Cetraben lotion	Diprobase cream	Doublebase gel	Diprobase ointment
		QV lotion	Epimax cream	Isomol gel	Emulsifying ointment BP
		Diprobase lotion	Aquamax cream	Zerodouble gel	White soft/Liquid paraffin 50/50 ointment
			Zerobase cream	AproDerm gel	Paraffin White soft ointment
			AproDerm cream	MyriBase gel	Paraffin Yellow soft ointment

† Membership be monitored and adapted over time, keeping within the inclusion and exclusion criteria for each group.

The approach of not naming specific emollients allows flexibility in the future, should new emollients be introduced/substituted for existing ones, i.e. if a new on-formulary product meets the group rules, the research team could add this to the list of emollients that participants be prescribed in that group, for the particular formulary/CCG.

13.3 Packaging and labelling

There is no additional trial-specific packaging or labelling as part of this study, and commercial packs of the products will be issued by pharmacies, as per usual care.

13.4 Storage, dispensing and return

As the commercial packaging and labelling will be unchanged, commercial recommendations for storage will apply.

Once randomised, GPs at participating surgeries will prescribe an emollient from a list of products within the allocated type of emollient. This prescription will be made as per normal practice (on an FP10) and make it available for repeat prescription. The FP10 will be taken/sent to a pharmacy of their choice, where the pharmacist will check and dispense the emollient as normal.

The emollient container, if emptied during the study, can be disposed of as normal (domestic household waste collection). Parents will be advised to return any unused emollient to their pharmacy for disposal, as is usual.

13.5 Directions on use and assessment of compliance

In this pragmatic trial, the directions on use will be the same as in routine primary care, where clinician advice on emollient use often does not extend beyond what is written on the prescription, which may be backed-up with an information leaflet. The study emollient will be issued with directions to “Use twice daily and as required”. The CSO will give participants simple verbal advice and a one-page summary on emollient use (created by the research team) at the baseline visit.

Daily use of the study emollient will be collected by means of participant weekly and monthly questionnaires, as described in section 11.4. Quantity of study emollient prescribed will be obtained from the EMR (see 11.5).

14 Pharmacovigilance

14.1 Overview

This is a type A Clinical Trial of an Investigational Medicinal Product (CTIMP) trial, which is low risk because the use of the medicinal product is not higher than the risk of standard medical care. The products under investigation have been used widely for many years and are available over-the-counter without a prescription.

The CI will provide (in addition to the expedited reporting below) Development Safety Update Reports (DSUR) once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

14.2 Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

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

"Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

14.3 Causality

The assignment of the causality will be made by the Chief Investigator using the definitions in Table 4 below. Other clinicians (e.g. the participant's own GP) may be asked for advice in these cases.

Table 4: Assignment of causality between adverse events/reactions and study emollients

Relationship	Definition
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the emollient). There is another reasonable explanation for the event.
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the emollient). However, the influence of other factors may have contributed to the event.
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

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, and one of the discrepant views classifies the event as a SUSAR, the MHRA will be informed of all points of view.

14.4 Collection and reporting

Adverse event reporting will be in accordance with the University Hospitals (UH) Bristol "Safety Reporting Standard Operating Procedure". UH Bristol, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. Any questions concerning adverse event reporting should be directed to the TM in the first instance.

All AEs, from the time a signed and dated consent form is obtained until 52 weeks after randomisation will be recorded in participant's weekly/monthly questionnaires. All documented AEs will be collated and reviewed at the monthly Trial Management Group meetings.

14.4.1 Adverse events and reactions

It is expected that most AEs/ARs will be expected treatment-related AEs/ARs. The main side effects are adverse events related to their use, such as slips and falls, skin infections and localised reactions. The study emollient information sheet will explain the importance of wiping away any emollients from standing surfaces and taking extra care if used during bathing. Expected possible local skin reactions include:[36]

- Stinging
- Itching
- Burning sensation
- Worsening of eczema
- Tingling
- Redness/inflammation
- Swelling
- Dryness
- Pain
- Peeling of the skin
- Skin infection.

Data on expected AEs/ARs listed above will be collected via parent self-report. As they will be reported as outcomes for the trial, they will not be formally reported as an adverse event. Non-serious medical occurrences which cannot be causally related to trial participation (e.g. upper respiratory tract viral infections, diarrhoea and vomiting) need not be reported, as this would represent a significant burden of unnecessary data collection in this age group.

14.4.2 Serious Adverse Events (SAEs)

Children in this age range are expected to have a variety of SAEs that are not related to the intervention. These expected SAEs will not be routinely reported. Non-reportable expected events will include (but are not limited to):

- Lower respiratory tract infections, including bronchiolitis
- Urinary tract infections
- Exacerbation of asthma
- Fractures.

Expected SAEs that may be related to the study emollients will be asked about in the parent diaries and recorded, but not formally reported (unless they are longer in duration or more serious than expected). These include slip or falls (e.g. in bath resulting in a fracture, broken bone or hospital treatment) within the family due to study emollient used for the child.

The death of a participant will be considered an SAE, as will be any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a child's participation. Hospitalisations will be reported, with the following exceptions:

- For social reasons in absence of an adverse event
- For surgery or procedure planned before entry into the trial (must be documented in the study diary)

Any reportable occurrences (i.e. those that are i) related and unexpected, or ii) related and expected but longer in duration or more serious than expected), meeting the definition of SAEs will be reported using the Serious Adverse Event Form. These SAEs will be reported to the UH Bristol contact (research@uhbristol.nhs.uk) by the CI or a delegated member of the research team within 24 hours of their knowledge of the event. All SAEs that have not resolved by the end of the study (i.e. 52 weeks after randomisation), or that have not resolved upon discontinuation of the participant's participation in the trial, must be followed until any of the following occurs:

- the event resolves
- the event stabilises
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the trial drug or to factors unrelated to trial conduct
- when it becomes unlikely that any additional information can be obtained (participant or healthcare practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

14.4.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All relevant information about a SUSAR which occurs during the course of the trial and is fatal or life-threatening will be reported within seven days to the MHRA by UH Bristol, on behalf of the Sponsor, and the relevant ethics committee by the research team. The expectedness of an adverse event will

be determined by whether or not it is listed in the Summary of Product Characteristics and the study protocol.

All relevant information about a non-fatal or non-life-threatening SUSAR which occurs during the course of the study will be reported within 15 days to the MHRA by UH Bristol, on behalf of the Sponsor, and by the research team to the relevant ethics committee. The expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics and the study protocol.

14.5 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator, Regulatory Authority or Funder on the basis of new safety information or for other reasons given by the Trial Steering/Data Monitoring Committee, regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Trial Steering/Data Monitoring Committee, who will advise on whether to continue or discontinue the trial and make a recommendation to the Sponsor. If the trial is prematurely discontinued, no new participants will be recruited, but data collection will be completed on active participants.

If any urgent safety measures are taken, the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

15 Statistics

15.1 Sample size

As we have four groups, we conducted our sample size calculation to allow us sufficient power to pick up clinically meaningful differences in (n=6) pairwise comparisons subsequent to a global test:

	Lotion	Cream	Gel	Ointment
Lotion				
Cream	Comparison 1			
Gel	Comparison 2	Comparison 3		
Ointment	Comparison 4	Comparison 5	Comparison 6	

We aim to identify a minimum clinically important difference (MCID) in POEM scores of 3.0 between any two treatment groups. Despite observing a SD of 4.89 in the feasibility trial (Choice of Moisturiser for Eczema Treatment (COMET), POEM score at 12 weeks among those who self-referred and had a baseline POEM>2), we performed our sample size calculation using a SD of 5.5 to allow for the observed SD to be greater than 4.89. This will also allow for smaller differences to be detected should the observed SD be less than 5.5. Based on these, we estimated that we require 416 patients (104 in each group) in order to detect a difference of 3.0 in POEM scores between any two groups with 90% power and a significance level of 0.05 (after adjustment for multiple pairwise comparisons). This assumes equal numbers of children randomised to each group. To allow for 20% loss to follow-up, we propose recruiting 520 patients in total.

The 2012 paper by Schram and colleagues[37] determined a POEM MCID score of 3.4, but our POEM MCID of 3.0 is based on our feasibility trial data.[26] We employed five methods to determine POEM MCID (three anchor-based methods using the PGA as the anchor and two distribution-based methods), all suggesting a POEM score of around 3.0. While this is more conservative than the estimation by Schram et al., their data were from trials of adults with severe eczema, whereas ours used data from young children recruited in a primary care population – the majority of the participants were classified as suffering from moderate eczema (42%, baseline POEM classification). Designing the study to pick up a minimum difference of 3.0 will allow us to detect differences as small as this or larger differences as proposed by Schram et al.

15.2 Data analysis

The analysis and presentation of the trial will be in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines[38 39] and a full statistical analysis plan will be developed ahead of any statistical analysis of post-randomisation measures. A CONSORT diagram showing the numbers of people approached, eligible, recruited and randomised (with reasons for exclusions) will be produced. Numbers and characteristics of participants recruited will be tabulated, including eczema severity. Primary statistical analyses between the randomised groups will be conducted on an intention-to-treat (ITT) basis, where participants are analysed as randomised. Descriptive statistics will be used to assess balance between the randomised groups at baseline and will be presented as means and standard deviations for normally distributed variables, medians and inter-quartile ranges for any skewed variables, or frequencies and percentages for categorical variables.

The primary outcome of this study is POEM score assessed weekly up to 16 weeks. For this analysis, we will use linear mixed models (weekly observations (level 1) nested within participants (level 2)) to

explore whether there are differences in mean POEM scores between treatment groups after adjusting for baseline scores and all stratification and minimisation variables used in the randomisation. This approach allows incomplete cases (i.e. patients who did not complete all of their weekly scores) to contribute to the analysis. Therefore, all patients contributing at least one post-baseline observation will be included. The assumptions for the multilevel model will be checked and appropriate transformations will be considered if these are not met.

Pairwise comparisons will be conducted to identify which intervention groups differed. We will present – both in graphs and tables – all six pairwise differences with 95% confidence intervals. To account for multiple testing, we will use a modified alpha of 0.0083 (0.05/6 pairwise comparisons equivalent). Graphs will make clear those differences that are different to zero, thus highlighting where one emollient is superior to another, as well as the size of the difference.

Secondary outcomes will be analysed according to the data type and frequency of recording. Continuous outcomes measured at multiple time points will be analysed similarly to the primary outcome as described above. Continuous outcomes measured once after randomisation – such as EASI score – will be analysed using linear regression adjusting for baseline values where available. We will consider alternative methods should assumptions not be met.

Patterns of use of the study emollient and other eczema treatments will be explored in the first instance using descriptive statistics. Based on these findings, comparisons may be made between treatment groups. The quantity of study emollient used and parental satisfaction will also be described using descriptive statistics.

Descriptive analysis of safety endpoints (the proportion of children having skin infections and the number of slippage incidents) will be presented both according to randomised group and according to actual emollient use in the two groups. The statisticians will remain blinded to allocation and any safety events for the categorisation of emollient use.

15.2.1 Sensitivity analyses

We will explore patterns of missing data and consider possible mechanisms for this. Based on these and observed data, appropriate methods for imputing missing data will be considered in sensitivity analyses, including both “best” and “worst” case scenarios. Where assumptions are met, this may include multiple imputation by chained equations, for example. Should there be imbalance between treatment groups on important baseline characteristics, sensitivity analyses will be conducted where the main analysis will be repeated adjusting for these.

We are unable to pre-specify what constitutes “substantial contamination”, but we will study patterns of emollient use over time to establish a meaningful definition. If there is a substantial amount of contamination, we will carry out a per protocol analysis. As sensitivity analyses will be exploratory in nature, 95% confidence intervals and p-values will be presented but will be interpreted with due caution.

15.2.2 Subgroup analyses

Pre-specified subgroup analyses will investigate whether treatment effectiveness (POEM), acceptability and quality of life are modified by the following factors measured at randomisation:

- Parent expectation: As the primary outcome is patient-reported and may be subject to performance bias, we will also explore whether reported effectiveness is linked to low or high expectation of effectiveness (pre-randomisation) by performing analyses stratified on this variable.

- Age: We would like to explore whether there are treatment differences in younger (<2 years) and older patients (≥2 years)
- Disease severity: We would like to explore whether there are treatment differences between those with mild eczema versus those with moderate/severe eczema
- Diagnosis of eczema: We would like to explore whether there are treatment differences between children who do and do not fulfil the UK diagnostic criteria for atopic eczema

The statistical methods used in the primary analysis will be extended to incorporate interaction terms, to test null hypotheses of no variation in treatment effect across subgroups.

A Statistical Analysis Plan (SAP) will be developed, reviewed and approved by the TS/DM-C prior to any data analysis. The SAP will contain more detail around the planned primary, safety, sensitivity and subgroup analyses.

16 Data management

Formal procedures will be developed for each aspect of trial data management and entry. The database and randomisation system will be designed so as to protect patient information in line with the Data Protection Act 1998. Trial staff will ensure that participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centres. All documents will be stored securely and made accessible only to trial staff and authorised personnel.

Data will be anonymised as soon as it is practical to do so. Accordingly, each participant will be assigned a trial participant identification (ID) number, allocated at randomisation, for use on Case Report Forms (CRFs), questionnaires, other trial documents and the electronic database. CRFs are the data collection tool where all source data is recorded. CRFs will be treated as confidential documents and held securely in a secure, locked cabinet and/or password protected location in accordance with regulations. Only those personnel approved by the Chief or local Principal Investigators will have access to the CRFs.

Any questionnaire data completed on paper by the participant will be entered onto the study database in electronic form by a member of the research team. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. All parents will be consented using paper consent forms. Consent forms and paper CRFs will be stored and archived at the University of Bristol.

Patient identifiers will be kept on a separate system from the clinical data and data protection requirements will be further enforced by best practice trial management procedures. Following the end of the trial, the database will be cleaned and locked. Procedures will be developed to describe these processes.

Qualitative interview data will be transcribed verbatim, cleaned and anonymised, and imported into NVivo (or similar software package) for analysis.

During the course of the trial, a data archiving plan will be developed. At the conclusion of the trial and after the database has been locked, all data will be archived for five years in accordance with the Sponsor's and NIHR guidance. This will be in a secure location and available on request for audit and inspection by regulatory bodies. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

17 Quality assurance, auditing and inspection

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trials) Regulations 2004
- Research Governance Framework for Health and Social Care
- European Union Directive 2001/20/EC on clinical trials
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of participants are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible.

As the randomised treatments within this study do not differ from common usual clinical practice, risk-based monitoring will be implemented in line with a risk-assessment.

For the day-to-day delivery of the trial to required standard, a complete list of SOPs covering all trial activities will be drawn up and developed in conjunction with the Sponsor. These will be dated/version tracked and monitored/revised accordingly.

17.1 Accuracy of Case Report Forms

All data requested on the CRF will be recorded, checked and any missing data explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be inserted. If the item is not applicable to the individual case, "N/A" will be inserted. If any entry errors are made on the CRF, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialled and dated. Pencil and correction fluid will not be used anywhere on the CRF. If it is not clear why the change has been made, an explanation will be written next to the change.

Data collected on each subject will be recorded by the CSO. Each patient enrolled into the study must have the correct CRFs completed. The Principal Investigator will allow study staff access to any required background data from such records (source data e.g. medical records) on request.

If a participant withdraws from the study during the treatment phase, the reason will be noted on the withdrawal form in the study database and the patient will be followed-up as per protocol (see Section 11.4). If the participant becomes non-contactable and so it is not possible to determine the specific reason for their discontinuation in the study (i.e., passively withdraws), this will be recorded in the study database and any further follow-up will not be pursued. If the patient withdraws their consent to any further participation in the study (treatment and follow-up), this will be recorded on the study database and no further follow-up is required.

17.2 Case Report Form sampling

A random sample of 10% of CRFs will be checked against the computerised database and relevant source data for quality purposes. This percentage will be increased if a significant error rate (more than 10% of those checked) is found.

17.3 Direct access to source data/documents

The CI and study sites will allow monitors (from UH Bristol on behalf of the Sponsor), persons responsible for the audit and monitoring, representatives of the ethics committee and of the regulatory authorities to have direct access to source data/documents. This is reflected in the

participant information leaflet and consent form. Trial monitoring will be undertaken on behalf of the Sponsor by UH Bristol following their standard monitoring procedure.[a]

17.4 Insurance and indemnity

The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University.

The University of Bristol has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from overall management of the research by the University of Bristol.

[a] http://www.uhbristol.nhs.uk/research-innovation/information-for-researchers/setting-up-and-running-a-clinical-research-study/what-to-do-when-approval-is-received/monitoring/

18 Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including, but not limited to, the Research Governance Framework (RGF) and the Health Research Authority (HRA) guidance.

This protocol and related documents will be submitted for HRA review that includes the application to an NHS Research Ethics Committee (REC). Any subsequent protocol amendments will be submitted to the HRA, on the agreement of the Sponsor.

Annual progress reports will be submitted to the HRA/REC. The first report will be submitted 12 months after the date on which the favourable opinion was given, and thereafter until the end of the trial. A DSUR will be prepared annually for submission to the MHRA. Progress reports will also be submitted to the funder, in line with NIHR reporting requirements. Copies of these reports will be sent to the Sponsor prior to submission. Copies of all relevant reports will be made available to the TS/DM-C as appropriate.

Participant safety and adverse events will be reported on and discussed at all TMG and TS/DM-C meetings. Any significant adverse events will be reported to Sponsor when they are notified to the trial team and the chair of the TS/DM-C.

A declaration will be submitted to the REC within 90 days of the end of the study. A final report at conclusion of the study will be submitted to the NIHR, the Sponsor and the REC within one year of the end of the trial.

19 Project management

The study is hosted by Bristol CCG, and will be delivered by the University of Bristol as the Sponsor, in collaboration with partners at University of Nottingham, University of Southampton and UH Bristol. The Universities of Nottingham and Southampton will be recruiting centres, with Professor Kim Thomas and Dr Miriam Santer as the Principal Investigators, respectively. The trial has been designed in collaboration with and supported by the BRTC.

19.1 Trial Management Group (TMG)

The Trial Management Group (TMG) comprises all investigators, the trial manager, research and administrative staff, with input from patient/public representatives (see below).

Members of the TMG contribute to the trial in the following ways: trial design; trial centre recruitment and trial conduct; trial management; trial logistics and cost management; economic evaluation; trial methods; statistical data analysis; and publication. This research will also be overseen by a joint TS/DM-C (see Section 19.2).

The TMG will meet on a regular basis to oversee the management of the trial. The TMG will be provided with detailed information by the centre staff regarding trial progress. Meetings will be face-to-face with teleconference facilities for TMG members who are unable to be present.

19.2 Trial Steering/Data Monitoring Committee (TS/DM-C)

Because this is a low-risk trial, as per the COMET[15] and BATHE[40] trials, the funder has agreed that the roles of both guiding the TMG and monitoring trial data will be undertaken by a single joint committee, the TS/DM-C.

The role of the TS/DM-C will be to provide overall supervision of the trial on behalf of the NIHR. In particular, the TS/DM-C will focus on progress of the trial, adherence to the protocol, patient safety and consideration of new information. The committee will review the accruing data and assess whether there are any safety issues that should be brought to the Sponsor's or the participants' attention or any reasons for the trial not to continue. Terms of reference will be drawn up and agreed with members of the TS/DM-C.

Membership comprises of 4 four independent members: a chairperson who is a GP & experienced trialist, an academic, a biostatistician and a patient representative (parent of child with eczema)). There is one additional non-independent member who is a qualitative researcher. Non-independent members will not have any voting rights. The CI will attend all meetings, accompanied by the trial manager and other TMG/trial staff as appropriate. Observers from the NIHR HTA, the Sponsor and the host (Bristol CCG) will be invited to each meeting.

The TS/DM-C will meet four times over the course of the study. The first meeting will be to agree terms of reference, review the protocol and study timelines. It is proposed that the second and third meetings will be nine (coinciding with the end of the internal pilot) and 13 months into the recruitment and follow-up of participants; and the final meeting will be around month 36, when analysis is almost complete and the final report is being prepared.

19.3 Role of Sponsor and funder

The Sponsor (University of Bristol) will have overall responsibility for the initiation and management of the trial, but on a day-to-day basis this responsibility will be delegated to the chief investigator, trial manager and trial management group.

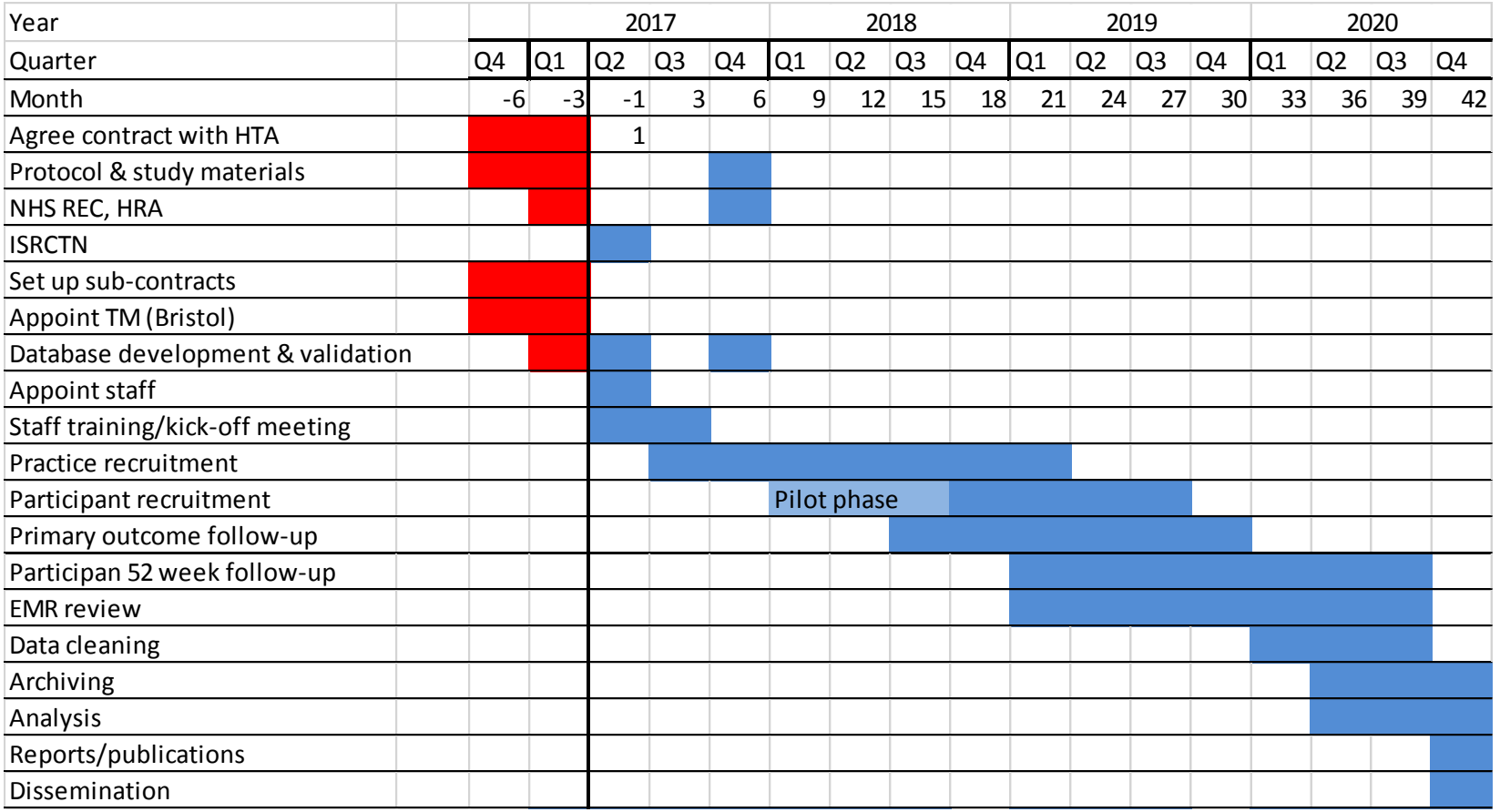
The funder (National Institute for Health Research) will remotely monitor study progress against key targets by means of reports from the TMG and TS/DM-C. They will review and approve outputs (abstracts, conference presentations, academic papers and final report) from the study, but will not seek to influence the reporting of findings. In this regard, the views expressed in the outputs will be those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

20 Timetable and milestones

20.1 Milestones

Month	Milestone
-1	NHS research ethic committee approval granted
-1	HRA approval and Capacity and Capability from NHS sites granted; Clinical Trial Authorisation (CTA) received
1	Full sponsorship granted by University of Bristol
3	Practice recruitment starts
9	Participant recruitment to internal pilot starts
13	Participant follow-up visits start
17	Internal pilot recruitment complete
26	Practice recruitment completed
28	Participant recruitment finishes
32	Participant primary outcome follow-up visits complete
40	EMR review complete
41	Data entry and cleaning complete
43	Analysis finished
44	Final report complete, papers submitted for publication, data archived

20.2 Study activities



21 Patient and Public Involvement (PPI)

We are dedicated to meaningful PPI throughout our research, from design to dissemination. Continued involvement by the parents of children with eczema will help the study to stay focused on delivering clinically important answers that are meaningful to patients, in an area that is not easy to research. Although the clinicians on the team have extensive experience and expertise in the treatment of children with eczema, previous research has highlighted the social and financial impact of this common condition. PPI will ensure that no professional "blind spots" occur in the conduct of this study. We recognise the importance of establishing and maintaining good relationships between researchers and lay representatives, and will work to achieve this through regular communication, managing meetings in order to address power imbalances and providing opportunities for informal engagement.

We will adopt a multi-pronged approach. First, Amanda Roberts is a PPI co-applicant with lived experience of eczema both as a patient and carer of children with eczema. She interacts with carers of children with eczema daily on behalf of the Nottingham Support Group for Carers of Children with Eczema through the Twitter feed @eczemasupport. She has also previously been involved in this capacity on other primary care eczema trials (CREAM, BATHE). She has agreed to attend TMG meetings, and has fully participated in the development of the grant proposal and this protocol. Second, we will continue to work with a group of parents of children with eczema local to the lead centre, who have been involved in various ways in developing this study and who want to support our on-going work through face-to-face/telephone meetings and email updates/requests. Planned meetings and purpose (all face-to-face except meeting 3), detailed in terms of project stage are:

1. An initial meeting to review the findings from the feasibility study; discuss aims and design of main trial; agree terms of reference and to involve the group in the development of the protocol and design of study materials
2. During the pilot phase, to review progress and to discuss/problem solve any issues (for example slow recruitment, adherence, protocol deviations)
3. At the half-way point during recruitment, aims as per meeting 2
4. At the end of recruitment, to discuss analysis and dissemination, planning pathways to impact
5. At the end of the study, to assist with lay summaries and presentation of findings at local and national events

Third, PPI involvement and support through the UK Dermatology Controlled Trials Network (UK DCTN) patient panel. The UK DCTN/Centre for Evidence Based Dermatology (CEBD) will provide support and training for all PPI members via their "patient panel" training days. In addition, to augment the other PPI work and maximise diversity, over 20 of their members will be invited to review/comment upon aims, materials, design, delivery and dissemination as required. Fourth, there is a PPI member on the TS/DM-C. Finally, building on experience gained from the feasibility trial in the use of social media to promote wider patient engagement, we will have a PPI section on the study website, a Facebook page and Twitter account. This will facilitate rapid surveys via Twitter/Bristol Online Survey (www.onlinesurveys.ac.uk) if we need swift input from a wider group of eczema patients. To maintain continuity and build on the established following of 197 people, the established feasibility trial Twitter account (@cometstudy) will be changed to the new study acronym (@beestudy).

We have involved the Centre for Academic Primary Care Patient and Public Involvement and Engagement coordinator in planning, and costed in time for their continued involvement throughout

the study to facilitate all this activity. We will summarise, appraise and evaluate PPI in the final report.

22 Publication and dissemination policy

A BEE publication policy will be developed in line with the University of Bristol guidance. Any trial-related media releases, publications and conference presentations will be submitted to the NIHR HTA for approval prior to publication. All publications will acknowledge the support of the NIHR HTA in funding this trial and include the Department of Health disclaimer. Outputs reporting elements of the trial that involved recruited participants should also acknowledge the CRN. Publications will additionally acknowledge the BRTC.

23 Amendment history

Record of protocol version numbers and amendments:

Version		Notes
Number	**Date**	
1.0	21.03.2017	Submitted for approval (March 2017) and approval received from REC, MHRA and HRA.
2.0	27.06.2017	Title page: ISRCTN, NHS REC, and NIHR portfolio numbers added; 10.3: Clarification of eligibility confirmation; 10.6: "Blinding to treatment allocation" table amended to reflect changes in research team/processes to minimize un-blinding of TMG members, in accordance with TS/DM-C recommendation; 12.3: Clarification that first set of interviews will be with participants during their first four weeks in the study, not during the first four weeks of the life of the trial itself; 19.2: clarity to TS/DM-C composition/roles; 14.3: clarification about who makes decisions regarding causality of adverse events/reactions.
3.0	03.08.2017	Clarification that screening POEM must be within 28 days of recruitment. Removal of signature page to separate document.
3.3	23.10.17	"Track changes" version uploaded to HTA as part of application to amend study intervention.
4.0	03.11.17	Amendment to the intervention, from 4 specific emollients, to type of emollient. Correction of minor typos. Clarification of Safety reporting section.

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