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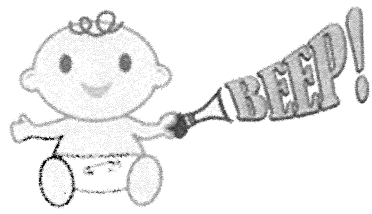

A randomised controlled trial to determine whether application of emollient from birth can prevent eczema in high risk children.

Statistical Analysis Plan

Final version 1.0
05 Dec 2018

Based on Protocol version 6.1 (dated 20 Oct 2017)

ISRCTN 21528841

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Lucy Bradshaw	Author	L Bradshaw	05-Dec-2018
Prof Alan Montgomery	Senior Trial Statistician	A Montgomery	5 Dec 2018
Professor Hywel Williams	Chief Investigator	Hywel Williams	5/12/18

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Abbreviations

Abbreviation	Description
BEEP	Barrier Enhancement for Eczema Prevention
CACE	Complier Average Causal Effect
CEBD	Centre of Evidence Based Dermatology
EASI	Eczema Area and Severity Index
POEM	Patient Orientated Eczema Measure
SAP	Statistical Analysis Plan
SPT	Skin Prick Test
TMG	Trial Management Group
TSC	Trial Steering Committee
UKWP	UK Working Party

Changes from protocol

The table below details changes to the planned analyses in the SAP compared to protocol version 6.1 (dated 20th October 2017).

Protocol section	Protocol text	Change	Justification
Maintenance of randomisation codes and procedures for breaking code, page 17	All researchers will be asked to record unblinding at the 24 months visit which will be used to inform a sensitivity analysis.	No sensitivity analysis will be conducted for unbinding at 24 months	The TMG discussed this during the development of the SAP as it was noted that unblinding of the researchers would only affect one component of the UKWP diagnostic criteria (visible flexural dermatitis). The rest of the criteria are reported by parents who it was not possible to blind. It was therefore decided that a sensitivity analysis according to unblinding would not be sensible for the primary outcome. Unblinding at 24 month visits will be reported as described in Section 5.4.
Statistics, methods, page 30	There will be two database locks for this trial. The first will be after all 24 month data have been received and checked. Analysis of the primary, secondary and safety end points will then be performed. The second database lock will be after all 60 months data (the longer term follow-up) have been received and checked.	Reporting of the trial will take place in two stages: the first for all 24 month data and the second for 60 month data. At 24 months, the database lock and analysis will proceed in two steps. The treatment allocations will be released to the trial statistician and the analysis will begin once all data at 24 months relating to the primary and secondary eczema outcomes has been cleaned and locked. Data relating to the food allergy outcomes will be locked and analysed in the second step.	The decision to lock the database at 24 months in two steps was made in order to expedite the main trial publication. This strategy was discussed and approved by the TSC.

Protocol section	Protocol text	Change	Justification
Statistics, methods, page 31	The analysis of eczema severity assessed using the POEM at 12 and 24 months and using the EASI at 24 months will include only children who develop eczema.	Analysis of eczema severity will include all children with data available on these assessments.	During SAP development, it was discussed that the burden of atopic eczema for health care use was in relation to moderate to severe cases. Therefore it was decided that analysis of eczema severity would be based on the binary outcome of a score indicating eczema of at least moderate severity and will include all participants with data on these assessments in the denominator (described in Section 6.5.3).

Amendments to versions

Version	Date	Change/comment	Statistician

Additional contributors to the SAP (non-signatory)

Name	Trial role	Job Title	Affiliation
Dr Robert Boyle	Co-investigator Lead clinician for food allergy component	Clinical Reader in Paediatric Allergy	Imperial College London
Dr Jo Chalmers	Co-investigator	Senior Research Fellow	Centre of Evidence-Based Dermatology, University of Nottingham
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1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the HTA funded randomised controlled trial to determine if application of emollient from birth can prevent eczema in high risk children (NIHR HTA reference: 12/67/12). The first version of this document will detail the analyses planned for the outcomes up to 24 months. The plans for the analyses of the tertiary outcomes collected at 36, 48 and 60 months will be detailed in a future revision of the SAP.

A separate document describes the analysis plan for the two by two factorial randomised sub-study of interventions to improve participant retention embedded within BEEP.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

Title	A randomised controlled trial (RCT) to determine whether application of emollient from birth can prevent eczema in high risk children.
Acronym	BEEP
Short title	Barrier Enhancement for Eczema Prevention
Chief Investigator	Professor Hywel Williams
Objectives	The primary objective is to determine whether advising parents to apply emollient to their child's skin for the first year of life in addition to best practice infant skin care advice can prevent the onset of eczema in high-risk children, when compared with a control group who are given the best practice infant skin care advice only. Secondary objectives are to determine any difference in the time to onset of eczema, the severity of eczema, the risk of food allergy, the risk of allergic sensitisation to food or non-food allergens, the onset of other allergic diseases, safety issues associated with the emollient, cost effectiveness and long term effects of the intervention.
Trial Configuration	The trial is a pragmatic, randomised, controlled, parallel group, multicentre assessor-blind trial.
Setting	Parents will be recruited from primary and secondary care as well as through general publicity and advertising and will be asked to follow the skin care advice for their child at home with minimal clinical contact.
Sample size estimate	Assuming that 30% of children in the control group will have eczema between one and two years of age and that a relative reduction of 30% is deemed to be of clinical importance (i.e. 21% of children in the intervention group have eczema between one and two years of age), a total of 1282 children will allow this difference to be detected at the 5% significance level (two-sided) with 90% power. This assumes equal numbers of children randomised to each group and 20% attrition. Up to 1400 children may be randomised following advice from the independent Trial Steering Committee after a planned sample size review after 20 months of recruitment
Number of participants	Maximum of 1400 children
Eligibility criteria	**Inclusion criteria**: • Child has a first degree relative with parental reported, doctor diagnosis of eczema, hayfever or asthma. • Child up to 21 days old. • Mothers must be aged ≥16 years • Consenting adult has the ability to understand English. **Exclusion criteria**: • Preterm birth (defined as birth prior to 37 weeks gestation). • Sibling (including twin) previously randomised into this trial. If multiple births the first child will be randomised into the trial.

	• Child has severe widespread skin condition that would make the detection and/or assessment of eczema difficult. • Child has a serious health issue which, at parent or investigator discretion, would make it difficult for the family to take part in the trial. • Any condition that would make the use of emollient inadvisable or not possible.
Description of interventions	All parents will be given best practice infant skin care advice for their child. Those randomised to the intervention group will, in addition, be advised to apply emollient daily to the child's entire body surface area for the first year of life. Parents of children in the intervention group will be given a choice of two emollients (Doublebase Gel® and Diprobase Cream®) and may change between the two emollients throughout the trial if they wish.
Duration of trial	The primary end point of the trial will be measured when the child is two years of age and the children will be followed up annually thereafter until they are five years of age. The additional skin care advice is only for the first year of the trial.
Randomisation and blinding	Randomisation will be to best practice infant skin care advice only (control) or to best practice infant skin care advice **plus** advice to use daily emollient (intervention). The randomisation schedule will be stratified by recruitment centre and number of immediate family members with atopic disease and based on a computer generated pseudo-random code using random permuted blocks of varying size. Although it is not possible to blind parents as to which group they are in the primary outcome at two years will be conducted by a researcher blinded to treatment allocation.

Outcome measures (between birth and 24 months as listed in protocol)	The primary outcome is a diagnosis of eczema between 12 and 24 months of age (defined as meeting the UK Working Party Diagnostic criteria).
	
	The secondary outcomes are:
	• Presence of eczema between birth and 24 months:
	  ○ Any parental report of a clinical diagnosis of eczema.
	  ○ Completion by parents of UK Working Party Diagnostic Criteria for Atopic Dermatitis at 12 and 24 months.
	• Presence of visible eczema at 24 months (skin examination by researcher).
	• Time to onset of eczema:
	  ○ First parental report of a clinical diagnosis of eczema.
	  ○ First topical corticosteroid and /or immunosuppressant prescription for eczema.
	• Severity of eczema:
	  ○ Eczema Area and Severity Index (EASI) at 24 months.
	  ○ Patient Orientated Eczema Measure (POEM) at 12 and 24 months.
	• Presence of other allergic diseases:

	○ Parental reported wheezing and allergic rhinitis between 12 and 24 months. ○ Parental report of a clinical diagnosis of food allergy at 12 and 24 months. ○ Parental report of food allergy at 12 and 24 months. Parents will be specifically questioned about cow's milk, egg, peanuts, and other nuts plus "any other food". ○ Allergic sensitisation at 24 months to any of the following common allergens: milk, egg, peanut, cat, grass pollen, house dust mite. ○ Confirmed diagnosis of food allergy at 24 months to milk, egg, peanut or 'any of milk, egg or peanut'. The diagnosis is derived from a combination of parental report, allergic sensitisation and food challenge. • Health-related quality of life : ○ CHU-9D at 24 months in order to estimate QALYs. ○ Parental quality of life measured using the EQ-5D-5L at baseline and 24 months in order to estimate change in parental QALYs, if any. • Health economic outcomes: ○ Health care resource use at 3, 6, 12, 18 and 24 months. ○ Cost effectiveness and cost-utility at 24 months (combining health resource use and health-related quality of life outcomes). The safety outcomes are: 1. Number of skin infection events during the first year. 2. Number of infant slippage incidents (slippage in hand and slippages to the floor) that occur within an hour of applying emollient during the first year.
Tertiary outcomes	1. Presence of eczema in the previous year at 36, 48 and 60 months based on parental report of a clinical diagnosis of eczema. 2. Any parental report that in their opinion their child has eczema at 3, 6, 12, 24, 36, 48 and 60 months. 3. Severity of eczema at 36, 48, and 60 months as measured by POEM* 4. Presence of other atopic diseases: a) Parental reported wheezing, allergic rhinitis and food allergy symptoms at 36, 48 and 60 months. b) Parental report of a clinical diagnosis of asthma or allergic rhinitis by 60 months. c) Parental report of a clinical diagnosis of food allergy at 36, 48 and 60 months 5. Health-related quality of life : a) CHU-9D at 36, 48 and 60 months in order to estimate QALYs.

	b) Parental quality of life: EQ-5D-5L at 36, 48 and 60 months in order to estimate parental QALYs. 6. Health economic outcomes: a) Health care resource use at 36, 48 and 60 months. b) Cost utility and cost effectiveness at 60 months (combining health resource use and health-related quality of life outcomes). *In children who have either a parental report of eczema or a parental report of a clinical diagnosis of eczema.

2.1. Sample size and justification

The sample size is based on assuming 30% of children in the control group will have eczema between one and two years of age (based on previous epidemiological studies in this high risk population) and a conservative relative reduction of 30% in the intervention group. This relative reduction is considered conservative as in the pilot study, a 50% reduction in eczema at 6 months was observed (43% developed eczema in the control group (n = 55) and 22% developed eczema in the emollient group (n = 53), 95% CI 0.28 to 0.9). The anticipated effect size is lower in this study due to the more pragmatic study design and the longer term outcome assessment. Such a reduction would still have important implications for families and health services.

A total of 1282 children will allow this difference to be detected (i.e. 30% of children in the control group compared to 21% of children in the group receiving additional advice having eczema between 1 and 2 years of age) at the 5% significance level (2-sided) with 90% power. This assumes equal numbers of children randomised to each group and 20% attrition at 24 months.

A sample size review by the TSC was planned after approximately 21 months of recruitment to check the assumptions underpinning the sample size (the percentage of children in the control group with eczema and the percentage of children lost to follow up). It was agreed in the March 2016 TSC meeting, that if 1282 participants had been randomised prior to 21 months that recruitment should continue to allow the sample size to be reviewed and potentially increased without a break in recruitment. The TSC reviewed the sample size in August 2016. They advised that consent to the study should be permanently terminated but randomisation should continue for any women who had consented to the study who had not yet been randomised. Randomisation to the study closed on 19 November 2016 with 1395 participants randomised.

See Section 2.4 for further details of the sample size review.

2.2. Trial committees

Trial oversight is provided by the Trial Management Group (TMG) and Trial Steering Committee (TSC). A data monitoring committee was not required due to the low medical risk associated with the advice to use daily emollient for the first year in addition to best practice infant skin care advice.

The TSC also provides safety monitoring usually undertaken by the data monitoring committee during a closed session where safety outcomes, split by allocated group, are discussed.

2.3. Outcome measures

2.3.1. Primary outcome

A diagnosis of eczema between 12 and 24 months of age (defined as meeting the UK Working Party Diagnostic Criteria for Atopic Dermatitis).

The UK Working Party (UKWP) Diagnostic Criteria for Atopic Dermatitis are satisfied where there is:

An itchy skin condition in the last 12 months

Plus three or more of:

i. Onset below age 2 years*
ii. History of flexural involvement
iii. History of a generally dry skin
iv. Personal history of other atopic disease**
v. visible flexural dermatitis as per photographic protocol

* not used in children under 4 years

** in children aged under 4 years, history of atopic disease in a first degree relative may be included

The UKWP diagnostic criteria are collected during a face to face visit with a researcher at 24 months. Where a face to face visit is not possible the UKWP diagnostic criteria may be collected using other methods such as telephone, post, text or email (Fleming, Bodner et al. 2001).

The table below describes how the information needed for the components of the UKWP Diagnostic Criteria is collected at 24 months in BEEP.

Criteria	***Question***	***Derivation for meeting criteria***
An itchy skin condition in the last 12 months	"In the last year, has your child had an itchy skin condition?"	Response of "yes"
History of flexural involvement	"Has this skin condition ever affected the cheeks or the skin creases in the past"	Response of "yes"
History of a generally dry skin	"In the last year, has your child suffered from generally dry skin?"	Response of "yes"
Personal history of other atopic disease	N/A. All children in BEEP must have a first degree relative with a history of atopic disease as trial inclusion criterion	

Criteria	*Question*	*Derivation for meeting criteria*
Visible flexural dermatitis as per photographic protocol	"Does the child have a visible dermatitis in any of these body areas today?" – around the eyes, on the cheeks, side and front of neck, front of elbows, outer forearms, behind the knees, outer lower legs and front of ankles. This is assessed by the research nurse if the 24 month visit is conducted face to face or based on parental report is this is not possible	At least one response of "yes" for the body areas listed

As in BEEP all children are under 4 years and have a history of atopic disease in a first degree relative, children will be derived as:

- having a diagnosis of eczema between 12 and 24 months if:
    - There is a response of "yes" to "In the last year, has your child had an itchy skin condition?" **AND** the criteria are met for **TWO or more** of the following questions:
        - "Has this skin condition ever affected the cheeks or the skin creases in the past", "In the last year, has your child suffered from generally dry skin?" OR "Does the child have a visible dermatitis in any of these body areas today?"
- not having eczema if:
    - There is a response of "no" to "In the last year, has your child had an itchy skin condition?" **OR**
    - There is a response of "yes" to "In the last year, has your child had an itchy skin condition?" **but** the criteria are met for **less than two** of the following questions:
        - "Has this skin condition ever affected the cheeks or the skin creases in the past" **AND** "In the last year, has your child suffered from generally dry skin?" **AND** "Does the child have a visible dermatitis in any of these body areas today?"

2.3.2. Secondary outcomes

Presence of eczema between birth and 24 months

- Any parental report of a clinical diagnosis of eczema.

  At 3, 6, 12, 18 and 24 months, parents are asked "In the last xx months, has your baby/child been diagnosed with eczema by a doctor or a nurse?" and at 24 months parents are asked "Has your child ever been diagnosed with eczema by a doctor or nurse?"

Children will be derived as having a parental report of a clinical diagnosis of eczema between birth and 24 months if there is a response of yes at any time point or to the question about ever being diagnosed with eczema.

Children will be derived as not having eczema if there is no parental report of eczema between birth and 24 months and there is a response of no to the question at 24 months "Has your child ever been diagnosed with eczema by a doctor or nurse?".

- Completion by parents of UKWP Diagnostic Criteria for Atopic Dermatitis at 12 and at 24 months.

12 months

Parents are asked the questions as described in the table above for the primary outcome (section 2.3.1) on the 12 month questionnaire, the only difference being that the question for "visible flexural dermatitis" asks about "this itchy skin condition" rather than "visible dermatitis". The table below describes how the information needed for the components of the UKWP Diagnostic Criteria are collected at 12 months in BEEP. Eczema will be derived as described for the primary outcome in section 2.3.1.

Criteria	***Question***	***Derivation for meeting criteria***
An itchy skin condition in the last 12 months	"In the last year, has your baby had an itchy skin condition?"	Response of "yes"
History of flexural involvement	Has this itchy skin condition affected any of the following areas in the last year or is it affecting any of these areas today?	At least one tick for "affected in the last year" in one of the following body areas: around the neck, fronts of elbows, behind the knees, fronts of ankles, around the eyes or on the cheeks.
History of a generally dry skin	"In the last year, has your baby suffered from generally dry skin?"	Response of "yes"
Personal history of other atopic disease	N/A. All children in BEEP must have a first degree relative with a history of atopic disease as trial inclusion criterion	
Visible flexural dermatitis as per photographic protocol	Has this itchy skin condition affected any of the following areas in the last year or is it affecting any of these areas today?	At least one tick for "affected today" in one of the following body areas: around the neck, fronts of elbows, behind the knees, fronts of ankles, around the eyes, on the cheeks, outer forearms or outer lower legs.

24 months

As visible flexural dermatitis is assessed by the research nurse at the 24 month face to face visit (not by parents), the question only version of the UKWP Diagnostic Criteria will be used for this outcome at 24 months – itch plus two or more of the remaining four features described in Section 2.3.1 (also see https://www.nottingham.ac.uk/~mzzfaq/dermatology/eczema/Section2-2.html). As in BEEP all children are under 4 years and have a history of atopic disease in a first degree relative, at 24 months using the questionnaire version of the UKWP diagnostic criteria , children will be derived as:

- having eczema if:
    - they have had in itchy skin condition in the previous 12 months **AND** the criteria are met for **ONE** of the following:
        - history of flexural involvement in the previous year OR history of generally dry skin in the previous year
- not having eczema if:
    - they have not had an itchy skin condition in the previous year **OR**
    - they have had in itchy skin condition in the previous 12 months **but** there is no history of flexural involvement in the previous year and no history of generally dry skin in the previous year

Presence of visible eczema at 24 months (skin examination by researcher)

Children where a skin examination by a researcher is conducted at 24 months will be derived as:

- Having visible eczema if they meet the criteria for visible flexural dermatitis as per photographic protocol on the UKWP criteria for atopic dermatitis at 24 months (see table in Section 2.3.1)
- Not having visible eczema if they do not meet this criteria

Time to onset of eczema

- First parental report of a clinical diagnosis of eczema.

  This will be derived as either 3, 6, 12, 18 or 24 months according to the first time that parents answer yes to "In the last xx months, has your baby/child been diagnosed with eczema by a doctor or a nurse?"

- First topical corticosteroid and /or immunosuppressant prescription for eczema.

  At 3, 6, 12, 18 and 24 months, parents are asked "Has your baby/child been given any prescriptions to treat eczema in the last xx months?" and if yes, for the name of the treatment.

The free text specified for the name of the treatment will be reviewed by a Senior Research Fellow from the Centre of Evidence Based Dermatology (CEBD) and Nurse Consultant to classify as topical corticosteroid, immunosuppressant or other.

The time to first topical corticosteroid and /or immunosuppressant prescription for eczema will be derived as either 3, 6, 12, 18 or 24 months according to the first time that prescriptions for topical corticosteroids or immunosuppressants are reported for children with a parental report of a clinical diagnosis of eczema.

Severity of eczema

- Eczema Area and Severity Index (EASI) at 24 months

During the 24 month visit, the researchers conduct a skin examination to complete the EASI (Barbier, Paul et al. 2004).

The head and neck, upper limbs, trunk and lower limbs are assessed separately for key signs of erythema (E, redness), oedema /papulation (I, thickness), excoriation (Ex, scratching) and lichenification (L, lined skin) and rated on a scale of 0 (none) to 3 (severe) in steps of 0.5 (excluding 0.5). Each sign is assessed for the entire body region – for example a child may have grade 1 erythema in some areas, but grade 3 erythema in others. If that is the case, then the "average of the two" is taken and so the score becomes 2. Likewise, if they have some areas that are grade 2 and others that are grade 3, then the score becomes 2.5.

The percentage area affected within each body region is also assessed and scored as in the table below.

% area affected	None	1-9%	10-29%	30-49%	50-69%	70-89%	90-100%
Area category	0	1	2	3	4	5	6

An EASI score for each body area is then calculated as:

(E + I + Ex + L) x area category

The total EASI score is a weighted sum of the four EASI scores for each body area:

(0.2 x head & neck score) + (0.2 x upper limb score) + (0.3 x trunk score) + (0.3 x lower limb score)

The EASI score ranges between 0 and 72, higher scores indicating greater severity of eczema. EASI scores can be categorised into six severity bands (Leshem, Hajar et al. 2015) .

The number and percentage of children with a moderate or worse score on the EASI (≥ 7.1) will be formally compared between groups.

- Patient Orientated Eczema Measure (POEM) at 12 and 24 months

The POEM is included in the 12 month questionnaire and given to parents to complete at 24 months.

The POEM for children is a 7 question parent/guardian-reported measure of eczema severity and asks about the frequency of seven signs of eczema (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking and dryness) in the previous week (no days, 1 to 2 days, 3 to 4 days, 5 to 6 days, every day – scored 0 to 4 respectively) (Charman, Venn et al. 2004). The responses to the seven items are scored to create a total score ranging from 0 to 28, higher scores indicating greater severity of eczema. POEM scores can be categorised into five eczema severity bands (Charman, Venn et al. 2013).

The number and percentage of children with a moderate or worse score on the POEM (≥ 8) will be formally compared between groups.

Presence of other allergic diseases

- Parental reported wheezing and allergic rhinitis between 12 and 24 months.

Parental reported allergic rhinitis is based on the response to the following question asked at 24 months "In the last year, has your child had a problem with sneezing or a runny or blocked nose when he/she did NOT have a cold or the flu? "

Parental reported wheezing is based on the response to the following question asked at 24 months "In the last year, has your child had any wheezing or whistling in the chest?".

- Parental report of a clinical diagnosis of food allergy at 12 and 24 months.

Parental report of a clinical diagnosis of food allergy will be based on the response to the following question "In the last year, has your baby been diagnosed with any food allergy by a doctor?" asked at 12 and 24 months.

Parental report of a clinical diagnosis of food allergy at 24 months will be derived as:

- Yes if there is a response of yes to "In the last year, has your baby been diagnosed with any food allergy by a doctor?" at 12 or 24 months
- No if there is a response of no to "In the last year, has your baby been diagnosed with any food allergy by a doctor?" at 12 and 24 months
- Unknown otherwise

- Parental report of food allergy at 12 and 24 months. Parents will be specifically questioned about cow's milk, egg, peanuts, and other nuts plus "any other food".

  This will be derived according to the responses at 12 and 24 months to the questions "has your baby/child ever had a reaction to":

  - Food containing cow's milk
  - Food containing egg
  - Food containing peanut (note 12 month questionnaire just asks about reaction to nuts rather than peanut & other nuts separately)
  - Food containing other nuts
  - Other food

  At 24 months, the question about whether the child has ever eaten the food will also be used and children who have never eaten the food will be derived as not having a parental report of allergy to that food. At 24 months the questions about how soon the reaction occurred will also be used to derive parental report of immediate food allergy.

  The following outcomes will be analysed between groups:

Outcome	Derivation of parental report of food allergy	Derivation of no parental report of food allergy
Parental report of any food allergy (12 and 24 months)	Response of yes to at least one of the questions above	No parental report of a reaction to any food.
Parental report of food allergy to cow's milk, egg or nuts at 12 months	Response of yes to a reaction to food containing cow's milk, egg or nuts at 12 months	No parental report of a reaction to food containing cow's milk, egg and nuts at 12 months
Parental report of food allergy to cow's milk, egg or nuts at 24 months	Response of yes to a reaction to food containing cow's milk, egg, peanut or other nuts at 24 months	No parental report of a reaction to food containing cow's milk, egg, peanut and other nuts at 24 months

Outcome	Derivation of parental report of food allergy	Derivation of no parental report of food allergy
Parental report of immediate allergy to any common food allergen at 24 months	Parental report of a reaction within 2 hours of eating a common food allergen (defined as cow's milk, egg, peanut, other nuts, fish*, sesame*, wheat*, soya* or kiwi fruit*)	No parental report of a reaction to any food OR parental report of reaction more than 2 hours after eating a common food allergen OR parental report of reaction within 2 hours to a food which is not a common allergen.
Parental report of immediate allergy to milk, egg or peanut at 24 months	Parental report of a reaction within 2 hours of eating either milk, egg or peanut	For milk, egg and peanut: either no parental report of a reaction or parental report of reaction more than 2 hours after eating

* - Information on the name of the food reported where parents answer "yes" to the question about whether "child had a reaction to any other food" will be reviewed by the food allergy panel to determine if reaction due to fish, sesame, wheat, soya or kiwi fruit.

- Allergic sensitisation at 24 months to any of the following common allergens: milk, egg, peanut, cat, grass pollen, house dust mite.

  Allergic sensitisation is tested at 24 months using skin prick tests. Allergic sensitisation will be defined as longest wheal diameter of 3mm or more (Heinzerling, Mari et al. 2013).

  The following outcomes will be analysed between groups:
  - Allergic sensitisation to any of the above allergens
  - Allergic sensitisation to milk, egg or peanut
  - Allergic sensitisation to cat, grass pollen or dust mite

  The table below shows how these outcomes will be derived.

Outcome	Derivation of allergic sensitisation	Derivation of no allergic sensitisation
Allergic sensitisation to any allergen	Longest wheal diameter of 3mm or more to a least one of cow's milk, egg, peanut, grass pollen, cat or dust mite	Longest wheal diameter of less than 3mm for cow's milk, egg, peanut, grass pollen, cat and dust mite
Allergic sensitisation to cow's milk, egg or peanut	Longest wheal diameter of 3mm or more to a least one of cow's milk, egg or peanut	Longest wheal diameter of less than 3mm for cow's milk, egg and peanut

Outcome	Derivation of allergic sensitisation	Derivation of no allergic sensitisation
Allergic sensitisation to grass pollen, cat or dust mite	Longest wheal diameter of 3mm or more to a least one of grass pollen, cat or dust mite	Longest wheal diameter of less than 3mm for grass pollen, cat and dust mite

- Confirmed diagnosis of food allergy at 24 months to milk, egg, peanut or 'any of milk, egg or peanut'. The diagnosis is derived from a combination of parental report, allergic sensitisation and food challenge.

  Diagnosis of confirmed allergy to each of the above foods will be based on the food allergy panel decision using either the food challenge outcome or if this is not available a panel consensus based on the information available. The process around the allergy testing and diagnosis is outlined in the flowchart on page 28 of the protocol (version 6.1). The table below shows how the data collected will be used to derive whether a child has an allergy to each food.

FOOD ALLERGY	NO FOOD ALLERGY
1. Confirmed by oral food challenge OR 2. Panel consensus of food allergy (where oral food challenge not done)	1. Parental reported frequent and recent consumer of relevant food, and no reported history of reactions within 2 hours of consumption OR 2. negative SPT (0mm) OR 3. Passed oral food challenge (i.e. negative) OR 4. Panel consensus of no food allergy

  The following outcomes will be analysed between groups:
  - Diagnosis of allergy to milk
  - Diagnosis of allergy to egg
  - Diagnosis of allergy to peanut
  - Diagnosis of allergy to milk, egg or peanut.

  The main food allergy outcome is diagnosis of allergy to milk, egg or peanut.

Health related quality of life

Health related quality of life will be analysed as part of the economic evaluation. Further details will be provided in a health economic analysis plan.

Health economic outcomes

Health economic outcomes will be analysed as part of the economic evaluation. Further details will be provided in a health economic analysis plan.

2.3.3. Safety outcomes

Number of skin infection events during the first year

Parents are asked on the 3, 6 and 12 month questionnaires if their baby had had any skin infections since the last questionnaire and if so, the number and what it was (impetigo, folliculitis, boils, other (with free text to specify) or don't know).

The free text specified where other is ticked will be reviewed by the Chief Investigator and Nurse Consultant to classify as skin infection or skin problem not an infection (e.g. nappy rash) and the type of skin infection (bacterial, viral, fungal or other).

The number of skin infections for each child will be derived as the total number of skin infections reported on the 3, 6 and 12 month questionnaires. Skin problems which were not classified as infections will not be included. Skin infections where the parent did not know what type it was will be included (i.e. assumed to have been reported correctly).

Number of infant slippage incidents (slippage in hand and slippages to the floor) that occur within an hour of applying emollient during the first year.

Parents are asked on the 3, 6 and 12 month questionnaires: "In the last xx months, have there been any slipping incidents involving your baby within an hour of applying any skin care products to your baby?"

A child will be derived as having a slippage incident if there is a response of yes to the slippage incident question at either 3, 6 or 12 months. The number of slippage incidents for each child will be derived using the number of questionnaires where a slippage incident was reported. The number and percentage of participants having a slipping incident and the number of slippage incidents per child (one, two or three) will be reported.

Note: the questionnaire did not ask how many slippage incidents there had been.

2.4. Interim analysis

No interim analysis of the primary outcome is planned. Stopping rules relating to recruitment, adherence to the intervention and emollient use by the control group were specified in the protocol and monitored by the TSC.

Version 1.0 of the protocol (25th April 2014) specified that the assumptions underpinning the sample size would be checked by independent members of the TSC after approximately 21 months of recruitment (i.e. by checking the percentage of children with eczema in the control group and percentage with follow-up data). However the original target sample size of 1282 was exceeded prior to this point and the chief investigator requested that the sample size review therefore be brought forwards. At this point (13th July 2016), sites were told to stop consenting women to the BEEP study however randomisation continued for women who consented before this date prior to the birth of their baby. In August 2016, independent members of the TSC were sent details of the follow-up questionnaire completion rate in each group and parental reported medical diagnosis of eczema in the control group from the questionnaires by an NCTU statistician independent of BEEP. The TSC were asked to advise on whether consent and randomisation should continue. They advised that consent to the study should be permanently terminated but randomisation should continue for any women who had consented to the study who had not yet been randomised.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. Analysis set

The main approach for the analysis will be to analyse participants (children) as randomised regardless of adherence with the allocated intervention for all primary and secondary outcomes as described in the table below.

One participant randomised in error at 62 days after birth will not be included in the numbers randomised or any analyses. The family were not informed of the randomisation and were not contacted for follow-up between birth and 24 months.

Outcome	Analysis set
Primary outcome *Secondary outcomes for presence of eczema, time to onset of eczema, severity of eczema and presence of other allergic diseases*	Participants analysed according to randomised group regardless of adherence with the allocated intervention. Main analysis for each outcome will be for participants with outcome data collected (i.e. without imputation for missing data).

Outcome	Analysis set
Safety outcomes	All participants where at least one of either the 3, 6 or 12 month questionnaires was completed. Data will be presented according to: 1. randomised group regardless of adherence with allocated intervention and 2. for each questionnaire time point according to randomised group and parental reported emollient/moisturiser use (none/some/widespread)

Different definitions of eczema and of eczema severity are collected in BEEP. Data will be presented as reported which may mean that there appear to be inconsistencies for instance, there will be some children who do not meet the UKWP criteria but have a score of more than 0 on the EASI.

3.2. Derived variables

Information on derivations are specified in section 2.3, section 4, section 5 and section 6.

3.3. Procedures for missing data

Missing items in questionnaires

For missing items on the POEM questionnaire, the total score will be calculated according to guidance on the CEBD website:

- If one question is left unanswered this is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored.

See http://www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx.

Missing baseline data

Missing baseline data is expected to be rare. However any missing baseline scores in analyses using the baseline as a covariate will be imputed using the mean score at each centre in order to be able to include these participants in the analysis. These simple imputation methods are superior to more complicated imputation methods when baseline variables are included in an adjusted analysis to improve the precision of the treatment effect (White and Thompson 2005).

Missing outcome data

The primary analysis will be based on participants with available data for the primary outcome at 24 months with no imputation for participants with missing outcomes.

Sensitivity analyses will be performed to check the robustness of the conclusions to missing primary outcome data. The pattern of missing outcome data will be explored, overall and in the two groups. Sensitivity analyses will include:

- using information collected from GPs on eczema diagnosis as a substitute for the primary outcome
- multiple imputation using chained equations to impute missing outcomes under the assumption that outcomes are missing at random (i.e. dependent on observed data but not the unobserved outcomes).
- Further sensitivity analyses to explore the robustness of the conclusions if outcomes are assumed to be missing not at random.

Full details are given in Section 6.2.

Sensitivity analysis, including multiple imputation, will also be performed for missing outcomes for the main food allergy outcome (confirmed diagnosis of food allergy). Full details are given in Section 6.6.

3.4. Adjustment for recruiting centre

Analyses will be adjusted for randomisation stratification variables including the recruiting centre. The majority of participants were recruited through secondary care. A small number of GP surgeries in London were set up as individual centres. These GP surgeries will be treated as one centre for the adjustment in the analysis.

Some participants had moved at 24 months so were followed up at one of the other centres. The original recruiting centre will be used for adjustment in the analyses.

3.5. Timing of final analysis

Reporting of the trial will take place in two stages. The main publication will be prepared after 24 month follow-ups have been completed and the primary outcome, secondary outcomes and safety outcome have been analysed. Tertiary outcomes up to 60 months will be reported in a later publication.

At 24 months, the database lock and analysis will proceed in two steps. The treatment allocations will be released to the trial statistician and the analysis will begin once all data at 24 months relating to the primary and secondary eczema outcomes has been cleaned and locked. Data relating to the food allergy outcomes will be locked and analysed in the second step.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Participant flow

The flow of parents and children through the trial will be summarised in a CONSORT diagram that will include the numbers potentially eligible, number excluded with reasons, numbers consenting, numbers not randomised with reasons, numbers randomised to the two treatment groups, number adhering to the allocated intervention, number of children with follow-up at 24 months, reasons if 24 month follow-up was not completed and the numbers analysed for the primary outcome.

Adherence with the allocated intervention in the CONSORT diagram will be reported in:

- the intervention group as the number of children where parents reported widespread emollient use over the majority of the child's body at least 3 days per week at 3, 6 and 12 months (i.e. compliant with the advice to use the emollient, see Section 5.9)
- in the control group as number of children where parents did not report using moisturiser regularly (at least 3 days per week) all over the child's body up until the point eczema was reported or at 3, 6 and 12 months if baby did not develop eczema in the first year .

4.2. Baseline characteristics

The baseline characteristics of the two groups will be summarised with respect to:

- Family baseline characteristics: age of mother, singleton or multiple pregnancy, ethnicity of mother and father, number of children in the household, whether any furry pets live in the household and whether the mother took any antibiotics or regular probiotic supplements during pregnancy
- Family history of atopic disease: mother, father and full blood sibling's history of eczema, asthma and hayfever, number of first degree relatives with atopic disease (one, two, three or more) and number of first degree relatives with eczema (none, one, two or more).
- Baby baseline characteristics: sex, number of weeks gestation at birth, delivery method, season of birth and *FLG* genotype.

In addition, whether the screening visit took place before or after birth and the number of days between birth and randomisation will also be summarised.

Number of weeks gestation at birth will be derived using the estimated date of delivery and baby date of birth.

Season of birth will be defined as:

- Spring – born in March, April or May
- Summer – born in June, July, August
- Autumn - born in September, October, November
- Winter – born in December, January, February

Continuous data will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages.

4.3. Post randomisation characteristics

Information collected on follow-up questionnaires and at the 24 month visit on characteristics which may be associated with the development of eczema will be summarised to inform the interpretation of the results. Data will be summarised on:

- Washing/bathing practices between birth and 24 months
- Feeding practices between birth and 6 months and age in months that the child first had solid food
- Probiotic supplements between birth and 6 months
- Antibiotics given to the baby
- Furry pets in the household
- Use of dust mite reduction measures
- Whether the house is fitted with a water softener
- Water hardness

In addition information on whether the child regularly attends nursery or playgroup, whether there are any additional children in the household compared to when the child was born and the decile for index of multiple deprivation for the area the child lives in will be summarised.

Information from the questionnaire at 24 months on whether the child had ever eaten cow's milk, egg, peanut and nuts other than peanut and, if so, if they have consumed the food frequently or recently as well timing of introduction of the food will be summarised for each food type. The timing of introduction of the food will be summarised using the median number of months from birth (with the lower quartile, upper quartile, minimum and maximum) and in categories (before 4 months, between 4 and 6 months, between 7 and 12 months, between 13 and 24 months or after 24 months/never eaten).

5. ASSESSMENT OF STUDY QUALITY

5.1. Randomisation

Randomisation is stratified by recruiting centre and number of immediate family members with atopic disease (1, 2, or more than 2).

The number of participants randomised to the two treatment groups at each recruiting centre will be tabulated. The number of immediate family members with atopic disease will be tabulated as part of the baseline characteristics (see section 4.2).

The number of immediate family members with atopic disease entered at the time of randomisation will be tabulated against the derived number of family members with atopic disease based on the information entered onto the electronic case report form.

5.2. Questionnaire completion

Families are followed up by questionnaire at 3, 6, 12, and 18 months (which could be completed online, on paper or over the telephone with a researcher). For each time point, the number and percentage of families completing any of the questionnaire will tabulated in the two groups along with reason if the questionnaire was not completed. The relationship of the person completing the questionnaire to the child will also be tabulated (mother, father or other) and the number of months to questionnaire completion from birth will be summarised using the median, lower & upper quartiles, minimum and maximum.

In addition, the pattern of questionnaire completion at 12 months (the intervention period) will be tabulated to show the number of participants where none of the questionnaires were completed, the number where all of the questionnaires were completed and the specific questionnaires completed for the children where some but not all questionnaires were completed.

The total number of questionnaires completed at 18 months will also be tabulated (i.e. none, one, two, three or four).

5.3. 24 month visit completion

At 24 months, there is a face to face visit with the researcher for an examination of the child's skin for signs of eczema. If this is not possible then the visit may be conducted remotely e.g. telephone, text, email or post.

The number and percentage of families where the 24 month visit took place will be tabulated along with the type of visit (face to face, telephone, email or post, the main type will be reported if more than one type), who the visit was completed with, where the visit took place for face to face visits and reason if the visit was not done face to face.

The number of months from birth to the 24 month visit will be summarised using the median, lower & upper quartiles, minimum and maximum. This will be derived as:

(date of 24 month visit – date of birth)/30.5.

The number of visits taking place prior to 23 months, between 23 and 26 months and after 26 months will be tabulated. The number of visits taking place outside of the preferred window of 21 to 30 months after birth will also be tabulated.

Reasons why the 24 month visit was not completed will be tabulated and further information (if given) will be listed for children where consent was withdrawn or the 24 month visit was not completed for other reasons. For children where the 24 month visit was not completed, the number where key minimal data was able to be collected from the child's GP will be summarised.

5.4. Blinding of research nurses during the 24 month visit

For visits conducted face to face, researchers are asked if they became aware of which group the child was randomised to and if so when this was in relation to the skin examination (before, during or after). This information will be tabulated and the details provided of the circumstances leading to the unblinding will be listed.

5.5. Genetic study participation

Families are asked if they wish to consent to an optional genetic part of the study for FLG genotyping. If consent is given a saliva sample is collected at the 24 month visit by the researcher or if this is not possible, parents are left a kit and asked to return a saliva sample.

The number of families consenting to give the saliva sample, the number of saliva samples collected at the visit, reasons if the saliva sample could not be collected at the visit, if a kit was left with the family and the number of samples sent for testing will be tabulated.

Samples are tested for the four most prevalent *FLG* loss of-function mutations in the white European population (2282del4, R501X, S3247X and R2447X). The number of samples where a result was obtainable on *FLG* mutation will be tabulated for all children and in addition for the subgroup of children whose mother and father reported being of white European ethnicity since the mutations tested are population-specific.

The number of participants who can be included in the analysis for an *FLG* mutation will be summarised. Children will be able to be included if both parents are of white ethnicity and genotyping was successful or a mutation was detected (regardless of ethnicity).

5.6. Allergy testing

The process around the allergy testing is outlined in the flowchart on page 28 of the protocol (version 6.1). This includes skin prick testing at the 24 month visit if consent is given and food challenges for children where there is a possible allergy.

The number of families consenting to the skin prick test (SPT) and the number where the SPT was done at 24 months will be tabulated. Reasons will be tabulated if the SPT was not done after consent was given. The allergens not tested when the SPT could not be fully completed will be tabulated.

Data will be reviewed by the food allergy team for participants with a positive SPT to milk, egg or peanut or a history suggestive of food allergy. The number of children referred to the food allergy panel along with the number of participants invited to a food challenge for at least one food and for each of the foods will be tabulated.

The number of children where the food challenge took place will be tabulated for each of the foods. The number of months from birth to the food challenge for each food will be summarised using the

median, lower & upper quartiles, minimum and maximum. Unblinding at food challenges will also be reported. Reasons for food challenges not taking place will be tabulated. Data from the food challenge including total dose of food given, symptoms during the challenge and treatment given for reactions to the challenge will be tabulated.

For each food where a child is invited to a food challenge, the method used for the final diagnosis of whether there is food allergy will be tabulated (based on food challenge, based on panel consensus or unclear [possible allergy or allergy unlikely]).

5.7. Protocol deviations

The number of participants with protocol deviations as reported by research nurses on the electronic case report form will be summarised by treatment group along with the type of deviation. Protocol deviations will also be listed.

The summary and listing will be done separately for protocol deviations not relating to food allergy assessment process and protocol deviations relating to the food allergy assessment process.

5.8. Dispensation of emollient by pharmacy

Families randomised to the intervention group received a 500g pack of Doublebase Gel® and a 500g pack of Diprobase Cream® after randomisation. Families then placed orders for additional emollient packs with the NCTU which were processed by a central pharmacy.

The number of days between birth and the date the first emollient was sent to families and the number and percentage of families in the intervention group placing an order for additional emollient will be summarised, along with the number of orders made in the year after randomisation. The type of emollient chosen in the initial order will be tabulated and for families placing more than one order whether there were any switches in the emollient ordered during the year.

5.9. Adherence

For the intervention group

Parents were contacted approximately two weeks after randomisation by the NCTU to collect the date that the family started to use the emollient. Days between birth and first emollient use will be summarised using the mean, standard deviation, median, lower & upper quartiles and categorised as 3 days old or less, 4 to 7 days old, 8 to 14 days old, 15 to 21 days old, 3 to 6 weeks, more than 6 weeks, not known.

From the questionnaires at 3, 6 and 12 months, information will be tabulated on the usual frequency of emollient use, the body areas that the emollient was applied to, the usual number of applications per day and the reason if the emollient had not been used at all in the months since the last questionnaire.

Compliance in the emollient group at each time point is defined as wide spread emollient use over the majority of the child's body at least three or more days per week. Parents will be considered to have applied the emollient to the majority of the child's body if they indicate applying it to 2 or more of the 3 body areas asked about (face/neck, arms/legs or trunk). Compliance at each time point will be tabulated.

For the control group

From the questionnaires at 3, 6 and 12 months, information will be tabulated on contamination defined as use of a moisturiser or oil at least three days per week over most or all of the child's body since the last questionnaire. This will be derived as:

- Yes if parents select "3 - 4 days per week", "5 - 6 days per week" or "everyday" to the question "In the last xx months, how often have you usually applied these (moisturisers/oils) to your baby's skin?" and select "Over most or whole of the body" in response to "In the last xx months, where on your baby have you usually applied these moisturisers or oils?"

This will be done for all children and excluding children with a report of eczema by the time point of interest. A report of eczema on the questionnaire is defined as selecting a response of "yes" to "In the last xx months, has your baby been diagnosed with eczema by a doctor or a nurse?"

Compliance and contamination over the first year

Compliance and contamination over the first year of life will be described using an ordered categorical variable, as defined in the table below.

Level of compliance in the intervention group/ contamination in the control group	**Criterion for compliance/contamination met at the following time points**
Full	3, 6 and 12 months
Early onset application	3 months (with neither or only one of 6 or 12 months)
Late onset application	6 and/or 12 months (but not at 3 months)
None	Compliance/contamination criterion not met at any of 3, 6 or 12 months

Compliance/contamination will be summarised for the subset of participants with complete data on compliance/contamination (i.e. completed questionnaires at 3, 6 and 12 months) and for all participants using the assumptions for missing data described below.

1. Participants with no reported data on emollient/moisturiser use will be categorised as not compliant in the intervention arm and not contaminated in the control arm.
2. If participants miss a questionnaire(s) and go onto complete a subsequent questionnaire, missing emollient/moisturiser use will be based on the next subsequent observation carried backwards. For example if the 6 month questionnaire was missed for a participant in the

intervention group and they reported being compliant at 12 months then it will be assumed that they were also compliant at the 6 month time point. The rationale for this is that it is assumed that compliance is likely to decrease over time so this is conservative for the intervention group.

3. If participants complete questionnaires initially and miss later questionnaires (e.g. complete at 3, did not complete 6 or 12 or completed at 3 and 6, did not complete 12) then it will be assumed that there was no compliance (intervention) /contamination (control) for the later missed questionnaires.
4. Categorisation of compliance/contamination over the first 12 months following randomisation for participants with missing emollient/moisturiser use data will then proceed according the table above.

Summaries will be split according to:

1. allocated group and
2. allocated group and whether there was a report of eczema in the first year (yes, no or unknown).

A report of eczema on the questionnaire in the first year will be based on the response to "In the last xx months, has your baby been diagnosed with eczema by a doctor or a nurse?". For children with a report of eczema, compliance/contamination prior to the questionnaire that eczema was first reported will also be tabulated.

Both groups at 18 months and 24 months

The intervention period for the trial was one year and parents in the intervention group were only supplied with emollient during this time. Parents in both groups were therefore asked the same questions about applying moisturisers to the child's skin at 18 and 24 months.

At 18 and 24 months, information will be tabulated on use of a moisturiser at least three days per week over most or all of the child's body since the last questionnaire. This will be derived as:

- Yes if parents select "3 - 4 days per week", "5 - 6 days per week" or "everyday" to the question "In the last xx months, how often have you usually applied these (moisturisers) to your baby's skin?" and select "Over most or whole of the body" in response to "In the last xx months, where on your baby have you usually applied these moisturisers?"

6. ANALYSIS OF EFFECTIVENESS/EFFICACY

Analyses will be performed using Stata version 15 or above. All tests will be two-tailed with point estimates and 95% confidence intervals for the treatment effect presented. Participants will be analysed as randomised, regardless of adherence with allocation. No formal adjustment for multiple significance testing will be applied: secondary outcomes will be considered supportive to the primary analysis.

The derived number of family members with atopic disease from the information entered onto the electronic case report form will be used for adjustment in the analyses if this does not match what was entered at the time of randomisation.

Between group analyses will compare best practice skin care advice plus advice to use emollients (intervention) to best practice skin care advice alone (control).

6.1. Primary analysis

The primary analysis will estimate the relative risk of eczema between 1 and 2 years of age (as defined in Section 2.3.1) using the available data. The number and percentage of children with eczema will be summarised in each group. The relative risk will be estimated using Generalised Estimating Equations with the Binomial family and log Link, with an exchangeable correlation matrix to account for randomisation being stratified by centre and randomisation stratification variable of number of immediate family members with atopic disease (1, 2, or more than 2) included as a covariate. The difference in risk will be estimated using similar methods. The between-group estimates will be presented with a 95% confidence interval and p-value.

6.2. Sensitivity analysis of primary outcome

The relative risk and difference in risk with 95% confidence intervals will be presented for all sensitivity analyses.

6.2.1. Sensitivity analysis with adjustment for other baseline covariates

Baseline variables will be examined for imbalances between the two groups. Any characteristics where an imbalance is observed (based on comparison of summary statistics only, not statistical testing) will additionally be included as covariates in the model specified in Section 6.1.

6.2.2. Sensitivity analysis using data collected from GP records

Information collected from GP records will be used in a sensitivity analysis as a surrogate for the primary outcome for children where it is not possible to collect the information required for the UKWP Diagnostic Criteria for Atopic Dermatitis between 12 and 24 months.

Using the information collected from GP records, a child will be derived as:

- Having eczema between 12 and 24 months if:
    - a diagnosis of eczema was first made when the child was between 12 and 24 months OR
    - a diagnosis of eczema was first made when the child was less than 12 months old AND the child received a prescription for eczema between 18 and 24 months of age (Abuabara, Magyari et al. 2017)
- Not having eczema between 12 and 24 months if the criteria above are not satisfied

Between groups estimates for the risk of eczema including information collected from GPs will be estimated as described in Section 6.1.

6.2.3. Sensitivity analysis according to method of collection of the primary outcome data

Sensitivity analysis according to whether the UKWP criteria were collected during a face to face visit or remotely (telephone, post, text) will be conducted.

The number of children meeting the criteria for eczema between 12 and 24 months according to allocated group and between group estimates for the risk of eczema will be presented separately for outcomes collected during face to face visits and outcomes collected remotely.

6.2.4. Sensitivity analysis according to criteria used for visible dermatitis in the UKWP criteria

A sensitivity analysis will be conducted by replacing "visible flexural dermatitis" in the UKWP criteria with any visible dermatitis as flexural dermatitis (although more specific for atopic eczema) may under-estimate true eczema prevalence.

Any visible dermatitis will be defined as an EASI score of greater than zero. This information is only collected for participants who had a face to face visit at 24 months. Visible flexural dermatitis information will be used if an EASI assessment was not conducted.

6.2.5. Sensitivity analysis for missing primary outcome data

The main analysis of the primary outcome will use the available data with no imputation. Multiple imputation using chained equations will be used as a sensitivity analysis to include participants with missing primary outcome in order to explore their potential impact on the estimate of the treatment effect compared to the complete cases.

Variables used in the imputation model will be:

- centre, number of immediate family members with atopic disease
- baseline variables identified as predictive of drop-out (by examination only),
- variables to be used in subgroup analyses - number of FLG mutations (none, one or two), the number of immediate family members with eczema, water hardness, season of birth and regular use of probiotic supplements during pregnancy.
- Compliance and contamination in the first year of life
- Parental report of a clinical diagnosis of eczema at 24 months
- Parental report of immediate allergy to cow's milk, egg or peanut at 24 months
- Allergic sensitisation to cow's milk, egg or peanut
- Confirmed diagnosis of food allergy to any of milk, egg or peanut (for sensitivity analysis for missing outcomes for main food allergy outcome, see section 6.6.2)

Imputations will be done using chained equations (White, Royston et al. 2011) and separately for each randomised group if possible. If the imputation model fails to converge including the variables above, a simpler model will be used. The number of datasets imputed will be based on the proportion of participants with a missing outcome and will be at least 5. The results of the analyses on the imputed datasets will be combined using Rubin rules for multiply imputed data. This analysis will assume that unobserved outcomes are missing at random and depend on observed characteristics but not the unobserved outcomes.

The assumption that data are missing at random cannot be tested. Therefore further sensitivity analyses will also explore the robustness of the conclusion if missing data are missing not at random. This will include:

- Assuming that all participants in the intervention group with missing data are eczema free and all participants in the usual care group with missing data have eczema (i.e. best case scenario) and
- Assuming that all participants in the intervention group with missing data have eczema and all participants in the usual care group with missing data are eczema free (i.e. worst case scenario).

The analysis in Section 6.1 will be repeated to explore if the findings from this sensitivity analysis are similar to the main analysis and to inform how different the missing outcomes would need to be to alter conclusions from the main analysis.

6.3. Secondary analysis of primary outcome

6.3.1 Accounting for compliance and contamination in the two groups

To explore the effect of application of emollient in the first year of life in parents who would comply with the allocated treatment, the complier average causal effect (CACE) will be estimated for the primary outcome (Shrier, Steele et al. 2014). CACE models will be implemented as latent growth mixture models (Dunn, Maracy et al. 2005), with compliance/contamination status included as a training variable for estimating class membership.

Two separate analyses will be performed based on the degree of non-compliance/contamination as described in Section 5.9:

(1) full compliance over the first year of life – participants in the control group who meet the criteria for full contamination will be considered as always-takers.

(2) compliance within the first three months (i.e. in the full compliance or early onset application categories) – participants in the control group meeting the criteria for full or early onset contamination will be considered as always-takers.

6.4. Subgroup analysis of primary outcome

Planned subgroup analyses are as follows: (1) none, one or two *FLG* null mutations; (2) number of immediate family members with atopic disease (one, two, three or more); (3) number of immediate family members with eczema (zero, one, two or more). Subgroup analyses will be conducted by including appropriate interaction terms in the regression model for the primary outcome. The number and percentage of children with eczema will be summarised in each subgroup and allocated group. The interaction effect, 95% confidence interval and p-value for the interaction effect will be reported in a table. Subgroup specific intervention effects will be presented in a forest plot. The trial is powered to detect overall differences between the groups rather than interactions of this kind so these subgroup analyses will be regarded as exploratory analyses and interpreted with due caution.

The *FLG* subgroup analysis will include children whose mother and father report being of white ethnicity, since the mutations tested are specific to the white European population, and children with at least one mutation (regardless of ethnicity). For the purposes of this subgroup analysis each of the 4 mutations will be assumed to have an equivalent effect on eczema risk, as predicted from what is known about filaggrin.

Participants will be categorised into three groups according to their *FLG* genotype for the 4 most prevalent mutations (R501X, 2282del4, R2447X, S3247X):

- *FLG* +/+ (none of the four mutations above) – control cohort
- *FLG* +/- (carrying one *FLG* null mutation) – heterozygous for one of the mutations above
- *FLG* -/- (carrying two *FLG* null mutations) – homozygous for one of the mutations above or compound heterozygous for two of the mutations above

Note that some participants will not be able to be grouped as above if consent was not given for the genetic component or the saliva sample provided was not adequate to achieve genotype results for all 4 mutations. Since the number of children with two *FLG* mutations is expected to be small, the subgroup analysis for *FLG* will be repeated using two groups (no *FLG* mutations versus one or two *FLG* mutations).

The following additional subgroup analyses, not specified in the trial protocol, will also be conducted: (1) season of birth (defined as per section 4.2); (2) water hardness (dichotomised into hard/very hard and moderate/soft); (3) parental reported regular use of probiotic supplements during pregnancy (yes/no).

6.5. Secondary outcomes

The adjusted relative risk and difference in risk with 95% confidence intervals will be presented for all binary secondary outcomes using the analysis model specified for the primary outcome in section 6.1.

6.5.1. Presence of eczema between birth and 24 months and presence of visible eczema

The number and percentage of children in the two groups with:

1. Any parental report of a clinical diagnosis of eczema
2. Atopic dermatitis at 12 and at 24 months based on completion by parents of UKWP Diagnostic Criteria and
3. Visible eczema at 24 months

will be tabulated and formally compared between groups.

A sensitivity analysis will be conducted for any visible eczema at 24 months whereby those with only cheek involvement will be considered to not have visible eczema. This will be done because having eczema on the cheeks only at 2 years of age may represent a form of irritant contact dermatitis from saliva and food as well as a manifestation of true atopic eczema.

6.5.2. Time to onset of eczema

Time to onset of eczema will be presented separately according to:

- first parental report of a clinical diagnosis of eczema and
- first topical corticosteroid and /or immunosuppressant prescription for eczema.

The term eczema is used below to describe the approach for both of these definitions. A parental report of a clinical diagnosis of eczema is considered as a necessary condition to define onset of eczema according to a topical corticosteroid/immunosuppressant prescription for eczema.

Time to onset of eczema will be presented descriptively by showing the cumulative percentage of children with eczema at 3, 6, 12, 18 and 24 months in a bar graph. Children will be included in the denominator at each time point if either:

- eczema is reported on the questionnaire or at a previous time point
- parents responded that their child had never had a diagnosis of eczema at 24 months
- parents responded as no when asked if their child had had a diagnosis of eczema on all questionnaires up to and including that time point (i.e. if 24 month follow-up not completed).

The numbers included at each time point will be reported in a table along with the number of children with onset of eczema at each time point.

6.5.3. Severity of eczema

The severity of eczema in each group using the EASI at 24 months and the POEM at 12 and 24 months will be presented descriptively in each group using:

- mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations and
- frequency counts and percentages according to the severity bands

Note, at 12 months the following instructions are given in the questionnaire "You do not need to complete this section if your baby has never had eczema". Therefore if the POEM is not completed and the parent has not reported the baby suffering from eczema in the previous 6 months on the 12 month questionnaire then a POEM score of 0 will be used for the summary and will be presented in the clear/almost clear severity band.

The number and percentage of children with a score indicating eczema of at least moderate severity on the EASI at 24 months, POEM at 12 months and POEM at 24 months will be formally compared between groups.

6.5.4. Presence of other allergic diseases – allergic rhinitis and wheezing

The number and percentage of children in the two groups with:

1. Parental report of allergic rhinitis between 12 and 24 months and
2. Parental report of wheezing between 12 and 24 months

will be tabulated and formally compared between groups.

The number of children who also have itchy, watery eyes with the allergic rhinitis and the number of attacks of wheezing in the last year will also be tabulated.

6.5.5. Presence of other allergic diseases – parental reported food allergy and parental reported clinical diagnosis of food allergy

The number and percentage of children in the two groups with:

1. Parental report of clinical diagnosis of food allergy at 12 months
2. Parental report of clinical diagnosis of food allergy at 24 months
3. Parental report of any food allergy at 12 months
4. Parental report of allergy to cow's milk, egg or nut at 12 months
5. Parental report of any food allergy at 24 months
6. Parental report of allergy to cow's milk, egg or nut at 24 months
7. Parental report of immediate food allergy to common allergen at 24 months
8. Parental report of immediate allergy to cow's milk, egg or peanut at 24 months

will be tabulated and formally compared between groups.

The number of children with a parental report of clinical diagnosis of food allergy between 12 and 24 months, the total number of times the parent reports the child has reacted to any food at 24 months and allergy to specific foods at 12 and 24 months will also be tabulated.

Parental report of a clinical diagnosis of a food allergy will be unknown at 24 months for children whose parents did not complete the 12 month questionnaire and report that their child did not have a clinical diagnosis of food allergy between 12 and 24 months (as the child may have had a diagnosis

between birth and 12 months). For these children, multiple imputation will be used for the unknown information at 12 months. A sensitivity analysis for parental report of clinical diagnosis of food allergy at 24 months will then be conducted using the multiply imputed data. In addition for children with no 24 month follow-up, data on diagnosis of food allergy between 12 and 24 months is being collected from GPs where possible. This data will also be used in the sensitivity analysis.

6.5.6. Presence of other allergic diseases – allergic sensitisation

Allergic sensitisation to each of the allergens tested will be summarised using the median, lower and upper quartile for the longest wheal diameter as well as tabulated in categories (SPT longest wheal diameter 0mm, 1 to 2mm, 3 to 6mm and 7mm or more).

The number and percentage of children in the two groups with a longest wheal diameter from the SPT of 3mm or more for:

1. Any allergen
2. Cow's milk, egg or peanut
3. Grass pollen, cat or dust mite

will be tabulated and formally compared between groups.

6.5.7. Presence of other allergic diseases – confirmed diagnosis of food allergy

For each of cow's milk, egg, and peanut, the diagnosis of food allergy and how this was determined will be tabulated i.e.

- Not allergic based on parental report and/or SPT
- Not allergic by panel consensus
- Not allergic confirmed by challenge
- Allergic by panel consensus
- Allergic confirmed by challenge
- Unclear – possible food allergy
- Unclear – food allergy unlikely

For the main analysis of food allergy, children will be considered as:

- allergic if agreed by panel consensus or confirmed by challenge and
- not allergic based on parental report and/or SPT (i.e. they did not need to be referred to the food allergy panel for review for potential allergy as per flowchart 2 in the protocol) or as decided by the food allergy panel either by consensus or confirmed by challenge.
- Unknown (i.e. missing) otherwise

For the outcome of food allergy to any of milk, egg or peanut, children will be considered as:

- Allergic if they are allergic to at least one of milk, egg or peanut
- Not allergic if they are not allergic to all three foods
- Unknown (i.e. missing) otherwise

The number and percentage of children in the two groups with food allergy to cow's milk, egg, peanut or any of milk, egg or peanut will be tabulated and formally compared between groups.

6.6. Additional analyses of the main food allergy outcome

6.6.1. Sensitivity analysis for confirmed diagnosis of food allergy at 24 months including panel consensus decisions of unclear

For the sensitivity analysis food allergy will be derived as in Section 6.5.7 and in addition children will be considered as:

- allergic if the panel decision was "unclear – possible food allergy"
- not allergic if the panel decision was "unclear – food allergy unlikely"

The analysis of food allergy to cow's milk, egg, peanut or any of milk, egg or peanut will then be repeated.

6.6.2. Sensitivity analysis for confirmed diagnosis of food allergy at 24 months using multiple imputation

The multiple imputation model specified in section 6.2.5 will be used to impute missing outcomes for confirmed diagnosis of food allergy at 24 months to any of milk, egg or peanut (using the derivation in Section 6.5.7).

6.6.3. Secondary analysis for confirmed diagnosis of food allergy at 24 months accounting for compliance and contamination in the two groups

The analysis specified in section 6.3 will be repeated to estimate the complier average causal effect for the confirmed diagnosis of food allergy at 24 months to any of milk, egg or peanut.

6.6.4. Subgroup analysis for confirmed diagnosis of food allergy at 24 months

Subgroup analyses for confirmed diagnosis of food allergy at 24 months to any of milk, egg or peanut will be conducted for (1) none, one or two FLG null mutations (categorised as per Section 6.4); (2) number of immediate family members with atopic disease (one, two, three or more); and (3) number of immediate family members with eczema (zero, one, two or more). Subgroup analyses will be conducted by including appropriate interaction terms in the regression model for the main food allergy outcome. The number and percentage of children with confirmed diagnosis of food allergy will be summarised in each subgroup and allocated group. The interaction effect, 95% confidence interval and p-value for the interaction effect will be reported. The trial is not designed to detect interactions of this kind so these subgroup analyses will be regarded as exploratory analyses and interpreted with due caution.

7. ANALYSIS OF SAFETY

For each questionnaire time point, skin infections and slippage incidents since the last questionnaire will be presented by allocated group parental reported emollient/moisturiser use (none/some/widespread over the majority of the child's body at least three or more days per week).

A summary of the safety outcomes over the first year in the two groups will be presented descriptively by allocated group for children where at least one of the 3, 6 or 12 month questionnaires was completed. The following information will be presented:

- For skin infections
    - Number and percentage of children where there was at least one skin infection reported
    - Summary statistics for the total number of skin infections reported for each child
    - Breakdown of the type of skin infections by showing the number and percentage of children with at least one occurrence of each type at infection (impetigo, folliculitis, boils, other bacterial infection, other viral infection, other fungal infection)
    - Listing of all skin infections
- For slippages
    - Number and percentage of children where there was at least one slippage incident reported
    - For children where there was at least one slippage incident, the number of questionnaires where a slippage incident was reported (one, two or three)
    - Listing of all slippage incidents with information on what happened collected from the parents (the trial management team attempted to contact parents if a slippage incident was reported on a questionnaire)

The number of skin infections reported per child will be formally compared using Generalised Estimating Equations with a negative binomial family and log link with an exchangeable correlation matrix to account for randomisation being stratified by centre and randomisation stratification variable of number of immediate family members with atopic disease (1, 2, or more than 2) included as a covariate. The incidence rate ratio with 95% confidence interval will be reported. Slippage incidents are expected to be rare, therefore the percentage of children with at least one slippage incident will be formally compared between groups using the analysis model specified in Section 6.1 for the primary outcome. Formal comparison between groups will be conducted according to randomised group regardless of adherence with allocation.

8. TERTIARY OUTCOMES

Analyses for the tertiary outcomes at 36, 48 and 60 months will be described in a future revision of the SAP.

9. FINAL REPORT TABLES AND FIGURES

See separate dummy table document

- *For analysis at 24 months - BEEP dummy tables for analysis at 24 months final version 1.0 .*

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