The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

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

FINAL version 3.0

09 Oct 2015

Short title:	Barrier Enhancement for Eczema Prevention
Acronym:	BEEP
Trial Registration:	www.clinicaltrials.gov
ISRCTN:	ISRCTN 21528841
NRES reference:	14/WM0162
Trial Sponsor:	University of Nottingham
Sponsor reference:	14044
Funding Source:	NIHR HTA reference: 12/67/12

TRIAL / TRIAL PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Angela Shone
Head of Research Grants and Contracts
Research and Graduate Services
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Chief investigator:
(medical expert)

Professor Hywel Williams
Director of Centre of Evidence-Based Dermatology
Centre of Evidence-Based Dermatology
University of Nottingham,
King's Meadow Campus,
Lenton Lane, Nottingham, NG7 2NR
Phone: 0115 8231048
Fax: 0115 823 1046
Email: hywel.williams@nottingham.ac.uk

Co-investigators:

Dr Kim Thomas
Professor of Applied Dermatology Research
Centre of Evidence Based Dermatology
University of Nottingham
King's Meadow Campus
Lenton Lane, Nottingham, NG7 2NR
Phone: 0115 8468632
Email: kim.thomas@nottingham.ac.uk

Dr Matthew Ridd
NIHR Clinical Trials Fellow
School of Social & Community Medicine
University of Bristol
Phone: 0117 33 14557
Email: m.ridd@bristol.ac.uk

Professor Alan Montgomery
Professor of Medical Statistics and Clinical Trials
Nottingham Clinical Trials Unit
University of Nottingham
Phone: 0115 884 4953
Email: alan.montgomery@nottingham.ac.uk

Dr Matthew Leighton
Research Manager
Nottingham Clinical Trials Unit
University of Nottingham
Phone: 0115 823 1490
Email: matthew.leighton@nottingham.ac.uk

Dr Tracey Sach
Reader in Health Economics

Health Economics Group
Norwich Medical School
University of East Anglia
Email: t.sach@uea.ac.uk

Professor Jim Thornton
Professor of Obstetrics and Gynaecology
Faculty of Medicine & Health Sciences
University of Nottingham
Email: jim.thornton@notttingham.ac.uk

Dr Robert Boyle
Clinical Senior Lecturer, Paediatrics
Imperial College London
Email: r.boyle@nhs.net

Professor Michael Cork
Head of Academic Dermatology & Honorary Consultant
Department of Infection &Immunity
University of Sheffield
Email: m.j.cork@sheffield.ac.uk

Dr Eric Simpson
Associate Professor, Dermatology
Oregon Health & Science University
Email: simpsone@ohsu.edu

Mrs Sandra Lawton
Nurse Consultant Dermatology
Nottingham University Hospitals NHS Trust
Email: sandra.lawton@nuh.nhs.uk

Trial / Trial Statistician:

Miss Lucy Bradshaw
Nottingham Clinical Trials Unit
University of Nottingham
E-mail: lucy.bradshaw@nottingham.ac.uk

Trial / Study Coordinating Centre:

Nottingham Clinical Trials Unit
C Floor
South Block
Queens Medical Centre
Nottingham
NG7 2UH

SYNOPSIS

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 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.
Number of participants	1282 children will be required in total – 641 in each group
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 or to best practice infant skin care advice **plus** advice to use daily emollient. 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	The primary outcome is a diagnosis of eczema between 12 and 24 months of age (defined as meeting the UK Working Party Diagnostic criteria). Secondary outcomes are other measures of the development of eczema (parental report of a clinical diagnosis, parental completion of UK Working Party Diagnostic Criteria, and visible eczema at 2 years of age), severity of eczema, presence of other allergic diseases, quality of life, health care resource use and cost effectiveness, and safety endpoints (slippages and skin infections).
Statistical methods	All analyses will be carried out using Stata 13 or above. The primary statistical analysis will be a comparison of the proportion of children with eczema between one and two years of age, summarised using a relative risk with 95% confidence interval, from a generalised linear model adjusting for randomisation stratification factors. All supportive analyses and analyses of secondary/long term outcomes will be documented in the Statistical Analysis Plan which will be finalised prior to database lock and unblinding. This will include methods to deal with missing data and sub-group analyses.

ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator (overall)
CEAC	Cost Effectiveness Acceptability Curve
CRF	Case Report Form
DMC	Data Monitoring Committee
EQ-5D-5L	EuroQol five dimensions with five levels
FLG	Filaggrin
GCP	Good Clinical Practice
HRQL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
IDQoL	Infant Dermatology Quality of Life
NHS	National Health Service
NCTU	Nottingham Clinical Trials Unit
PedsQL	Paedeatric Quality of Life
P/GIS	Parent / Guardian Information Sheet
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
QALYs	Quality-Adjusted Life Years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TMG	Trial Management Group
TSC	Trial Steering Committee

TABLE OF CONTENTS

TRIAL BACKGROUND INFORMATION AND RATIONALE

Eczema (1) is a very common skin problem affecting 16% to 30% of UK children and around 20% worldwide (2, 3). Global surveys have shown that eczema is on the increase, but it is not clear why (4). Eczema usually starts in infancy and around 40% of cases persist into adulthood, especially those with early and widespread disease (5). Although all skin areas can be affected, eczema often starts on the cheeks and limbs and then settles in the skin creases. Constant itching results in skin damage and causes a vicious itch-scratch cycle. Scratching results in bleeding, secondary bacterial infection and sleep loss to the child and family. Damage from scratching may lead to autoimmunity developing against skin components which can lead to disease chronicity (6). Eczema is also associated with attention deficit hyperactivity disorder, perhaps as a consequence of severe disease in early life (7). Growth and puberty may be delayed in severely affected children. The stigma associated with a visible skin disease adversely affects the quality of life of the child and family, yet it is often trivialised as “only itchy skin”. The family impact of caring for a child with moderate or severe eczema is greater than that caring for children with type 1 diabetes mellitus, mainly due to sleep deprivation, employment loss, time to care for eczema and financial costs (8). In the World Health Organisation 2010 Global Burden of Disease survey, eczema was the commonest reason for disability adjusted life years (9). Eczema results in a high economic burden (10), with overall costs comparable to asthma (11). Families often incur additional costs for special clothing and creams (8, 12). A systematic review of 59 studies estimated that direct costs of eczema treatment in the US could be as high as $3.8 billion per year (12). Eczema is a chronic condition accounting for the highest number of new GP consultations in England for a skin complaint (13). Moderate to severe eczema often requires referral to secondary care. Guidelines for children with eczema were produced by the National Institute for Health and Care Excellence (NICE) in 2007 (14).

Relationship of eczema to other allergic diseases

Children with eczema, especially severe eczema, are at increased risk of also developing other allergic (immunoglobulin E (IgE)-mediated) diseases including food allergy, allergic asthma and allergic rhinitis (hayfever). Together these are the most common chronic diseases of childhood and represent a major financial burden to the National Health Service (NHS), with direct costs estimated at over £1 billion per annum in 2004 (15). Eczema is often the first manifestation of the so-called “atopic march”, in which a child progresses from eczema to food allergy, asthma and allergic rhinitis later in life (16, 17). Eczema is strongly associated with peanut allergy and sensitisation to other foods such as milk, eggs, soy, wheat and fish. Population-based cohort studies reveal that around one in three children with eczema go on to develop asthma, especially allergic asthma (18). Allergic rhinitis is usually the last of the allergic diseases to appear, and is about three times more common in children with eczema in early life (19). Around half of UK school children with eczema also suffer from allergic rhinitis (20).

Causes of eczema

Eczema is a complex disease caused by the interplay of multiple genetic and environmental factors. The early onset of disease, the rising prevalence and increased incidence of eczema in smaller families (21), those from a higher socio-economic background, and in those migrating from low prevalence countries to Western countries, suggests that environmental factors operating early in life play a critical role in determining disease expression (4, 22). The ‘hygiene hypothesis’ has been proposed to explain why allergic diseases are more prevalent in developed societies. This hypothesis suggests that a lack of stimulation of the developing immune system by microbes prevents its full maturation. However, experimental evidence for this hypothesis is still conflicting as the issues appear to be complex (23, 24).

Environmental risk factor studies have shown conflicting results and have not, to date, led to useful preventative strategies. Eczema is highly heritable and shows strong familial clustering. Although genetically-determined variation in cutaneous and systemic inflammation are important in eczema predisposition (25), common mutations in the gene encoding filaggrin, a key skin barrier protein, represent the strongest known genetic risk factor for eczema (26, 27). Filaggrin loss-of-function mutations are found in approximately 9% of the white European population; these individuals have a measurable reduction in their skin barrier function and a striking three-fold increased risk of atopic eczema (28). Approximately 40% of moderate or severe eczema cases in hospital practice carry one or more filaggrin loss-of-function mutations (29, 30).

Importance of the skin barrier

Although previous eczema research has focused on the role of the immune system in atopic inflammation, the strong association between filaggrin mutations and atopic eczema, as well as atopic asthma and allergic rhinitis, has re-ignited interest in the pivotal role of the skin barrier as the key early event leading to eczema development (6). A defective skin barrier allows water to be lost from the skin, resulting in a generally dry skin – one of the first abnormalities to be noticed in babies who eventually develop eczema (31). A recent cohort study showed that skin barrier dysfunction (dry skin and increased trans-epidermal water loss) can precede clinical skin inflammation and that filaggrin mutations are associated with these changes in infants even prior to developing eczema (3, 32), supporting the notion that the primary event in the development of eczema and atopy is a dysfunctional skin barrier. The skin barrier not only keeps useful things like water in, but also helps to keep out potentially harmful things such as irritants, bacteria and allergens. The use of harsh soap and detergents can raise the pH of the outer layers of the skin and disturb the fine balance of enzymes, proteins, lipids and micro-organisms on the skin surface (33). A rise in pH leads to further breakdown of the skin barrier and is therefore a common pathway through which genetic and environmental factors influence skin barrier function (33-35). Skin irritation from soaps and other wash products is worse in children with a pre-existing skin barrier defect. Such irritation can initiate skin inflammation (6) which is then perpetuated through autoimmune mechanisms (6).
Dry skin is very common in eczema (31) even in the absence of known filaggrin loss-of-function mutations. Skin barrier damage from wash products starts in early life, so there is good reason to promote enhancement of skin barrier function in early life in all children at risk of eczema. Those with filaggrin gene mutations simply represent the group with the most profound barrier disruptions who might benefit the most.

It is also possible that the skin is the primary organ for development of allergic sensitization. Even though allergens are too large to penetrate the skin directly, the defective skin barrier makes it easier for allergens to interact with skin cells such as Langerhans cells which are responsible for initiating sensitization (36).

Animal studies have suggested that IgE sensitization may occur via the skin. The observation that mutations in genes coding for the skin barrier proteins (such as filaggrin) are associated with peanut allergy independently of eczema (30) and that peanut oil on the skin during childhood may be a predictor of confirmed peanut allergy (37), further support the notion that the skin might be a primary route of sensitisation for food allergies. If true, then the skin barrier is a target for prevention of not only eczema, but also for food allergy and progression to asthma and allergic rhinitis in the atopic march.

Emollients and the skin barrier

Emollient (moisturiser) therapy improves the skin barrier function. An emollient provides lipids to the stratum corneum, which in turn, improves skin hydration by trapping in water. Emollients also help to prevent inflammation caused by external irritants as evidenced by

their benefit in preventing irritant occupational hand eczema (38). Emollients have been shown in premature babies to reduce the incidence of skin inflammation (39), to reduce flares of eczema (secondary prevention) and to decrease the need for topical steroids (40). Not all emollients are the same since they vary in their consistency, from greasy paraffin derivatives to lighter water-based creams.

Primary prevention and the NHS

Primary prevention is a highly desirable goal in a chronic disease like eczema with no cure. Parents with experience of eczema are often anxious to know whether their future children will develop eczema and what they can do minimise the risk (41). If primary prevention of eczema using a strategy of early skin barrier enhancement with simple low-cost emollients works, it would represent a significant cost saving for the NHS through reduced treatment and appointment costs, especially in those cases persisting into adulthood. Further cost savings would result if early skin barrier enhancement prevents sensitisation and associated food allergy, asthma or allergic rhinitis. Even if the frequency of eczema cannot be significantly reduced, a reduction in the severity distribution of eczema could reduce the distress to patients, the number of consultations in primary care and subsequent referrals to secondary care.

Other emollient prevention studies

A case control study conducted in Kenya published in 1991 suggested that petroleum had a protective effect against the development of eczema (42), but this study has not been followed up with a definitive RCT. One RCT from Bangladesh has shown that barrier enhancement from sunflower oil may reduce serious infections in preterm babies (43). A small Japanese pilot study (International Clinical Trials Registry Platform study ID: UMIN000004544) of 70 patients looking at emollients as a prevention strategy for eczema started in late 2010 but the results of this study have not yet been reported. Another small short-term pilot study conducted in Japan randomised 71 babies at high risk of atopic disease to skin care instructions (including emollients) versus no instructions, and found no difference in diagnosed eczema at 6 months. The group did however show that positive reaction to skin prick tests was lower in the intervention group (44). An open-label pilot study of emollient therapy from birth showed only 15% of high-risk infants developed eczema against an expected rate of 30 to 50% (45). This study also showed that emollient therapy was a safe and acceptable intervention.

We are not aware of any other definitive trials underway to evaluate the prevention of eczema through barrier enhancement after searching trial registries (WHO meta-register until December 18th 2013). We did find one commercial study (n=400) taking place in the US and Canada (NCT01577628) which is evaluating a cosmetic moisturiser containing shea butter, paraffin, waxes and vegetable oils (Lipikar Balm AP, Cosmetique Active International) for the prevention of eczema.

A pilot, multicentre, RCT was carried out to determine the feasibility of a large RCT, followed by a parent preference ranking exercise of emollients and mechanistic studies to look at the effects of emollients on the skin barrier to inform the choice of emollient(s) in the main RCT (REC Reference number - 09/H0407/43). (Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention)

TRIAL OBJECTIVES AND PURPOSE

PURPOSE

To determine whether advising parents to apply emollient to their child for the first year of life in addition to best practice infant skin care advice can prevent or delay the onset of eczema.

PRIMARY OBJECTIVE

To determine whether advising parents to apply emollient daily for the first year of life in addition to providing 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

- To determine whether there is a difference between the two groups in:-
    - The time to onset of eczema.
    - The severity of eczema that develops.
    - The onset of other allergic diseases (asthma, allergic rhinitis and food allergy).
- To establish any safety issues associated with the application of emollient.
- To determine whether emollients offer a cost effective strategy for the NHS.
- To determine whether any preventative effect is sustained into later childhood.

DETAILS OF PRODUCT(S)

Description

The emollient products used in the trial are Doublebase Gel® and Diprobase Cream®

Manufacture

Doublebase Gel® (PL 00173/0183) is manufactured by Dermal Laboratories Ltd and Diprobase Cream® (PL 00025/0575) by Merck Sharp & Dohme Ltd.

Packaging and labelling

There is no trial specific packaging or labelling for the emollients. Commercial packs of the products will be used. 500g packs will be normally be supplied although smaller packs may be supplied initially to enable parents to choose their preferred emollient.

Storage, dispensing and return

As the commercial packaging and labelling is used unchanged the commercial recommendations for storage will apply.
Once randomised to the intervention group parents will be advised how to order the emollients for the duration of the trial. Orders will be co-ordinated by the NCTU and processed by a central pharmacy registered by the General Pharmaceutical Council. Products will be sent to participants at their chosen address.

Any surplus emollient not used at the end of the trial will be disposed of/ used by the parents. It will be made clear to parents that the trial will only supply the emollient for one year.

Known Side Effects

Thicker emollients can sometimes cause inflammation and infection of the hair follicles (folliculitis). Contamination of the emollients with bacteria from the hands does not occur with the pump dispenser method of using the emollients chosen for this study. Slippage incidents are a further rare possibility as the combination of moisturisers and water can make the baby slippery, and some babies will be attempting to stand or walk by the age of one year. The patient information leaflet will explain the importance of wiping away any emollients from standing surfaces.

The known side effects for both emollients are local skin reactions as advised in the Summary of Product Characteristics.

Reference source: eMC website: https://www.medicines.org.uk/emc/default.aspx

TRIAL DESIGN

TRIAL CONFIGURATION

The trial is a pragmatic, randomised, controlled, multi-centre, assessor blind, parallel group trial. A total of 1282 participants will be recruited over a 24 month period with five year follow up and primary outcome assessed at two years.

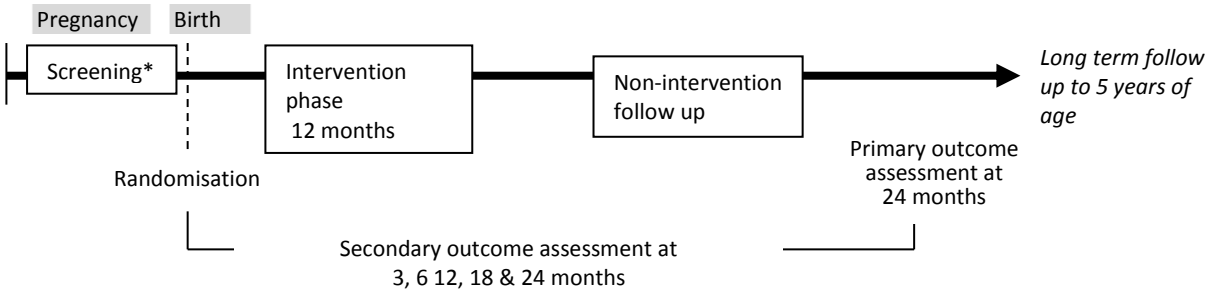
Screening will take place either during pregnancy or soon after delivery during a face-to-face visit with the researcher. Families will be randomised within 21 days of delivery of their baby to one of two groups in a 1:1 ratio:

- **Control Group:** Parents given best practice infant skin care advice only.
- **Intervention Group:** Parents given best practice infant skin care advice PLUS advice on how to apply emollient at least once a day for a year to their child's skin.

A two by two factorial randomised sub-study looking into retention rates will be nested within the trial. The interventions will be:-

- Compensation for parent's time in the form of £10 voucher – sent to parents either before or after the 24 month visit.
- Extra prior notification that the questionnaire is ready to complete via SMS text message versus no extra notification.

Figure 1 – Overview of trial design



*** Screening can take place either during pregnancy or within 21 days of delivery**

Primary endpoint

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

To reflect the chronicity of eczema, these criteria refer to signs and symptoms present over the past year. Applying the criteria at 24 months of age will therefore detect eczema present only between the ages of 12 and 24 months, thus excluding transient eczematous rashes which are common in the first year of life and often reported by parents as "eczema" but less likely to be true atopic eczema. The full criteria can be found in appendix 1.

Secondary endpoints

The secondary endpoints are:

1. 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.
2. Presence of visible eczema at 24 months (skin examination by researcher).
3. Time to onset of eczema:
    - First parental report of a clinical diagnosis of eczema.
    - First topical corticosteroid and /or immunosuppressant prescription for eczema.
4. Severity of eczema:
    - EASI at 24 months.
    - POEM*at 12 and 24 months.
5. Presence of other allergic diseases:
    - Parental reported wheezing, allergic rhinitis and food allergy symptoms between 12 and 24 months.
    - Parental report of a clinical diagnosis of food allergy at 12 and 24 months.
6. Health-related quality of life :
    - Infants' Dermatitis Quality of Life questionnaire $(IDQoL)^{+}$ at 24 months.
    - PedsQL 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.
7. 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).

*In children who have either a parental report of eczema or a parental report of a clinical diagnosis of eczema.

Safety endpoints

Safety endpoints will be:

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 endpoints

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. PedsQL at 36, 48 and 60 months in order to estimate QALYs.
6. Health economic outcomes:
    a. Health care resource use at 36, 48 and 60 months.
    b. Cost effectiveness and cost-utility at 36, 48 and 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.

Stopping rules and discontinuation

The following criteria will result in discussions with the Trial Steering Committee (TSC) and the funder (where appropriate) regarding the best course of action:

- ***Recruitment***: If recruitment (as documented in the recruitment plan) is less than 50% of the expected rate by 15 months, and strategies to overcome the identified barriers to recruitment have not been successful.

- ***Adherence to the intervention***: If fewer than 90% of families in the intervention group have applied emollient over the majority of their child's body at some stage *and* fewer than 70% are still using emollient at 6 months.

- ***Emollient use by the control group:*** If emollient use in the control group exceeds 25% of families at 6 months. This excludes the use of emollients for the *treatment* of eczema and only applies to emollient use that closely reflects the intervention (i.e. regular widespread use in the first year of life, defined as wide spread emollient use over the majority of the child's body at least three or more days per week).

RANDOMISATION AND BLINDING

The randomisation schedule is based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure (SOP) and held on a secure University of Nottingham server. The randomisation will be stratified by recruiting centre and number of immediate family members (parents or siblings) with atopic disease (1, 2, or more than 2).

Access to the sequence will be confined to the trial team at NCTU. Principal Investigators (PI) and researchers will access the randomisation website by means of a remote, internet-based randomisation system developed and maintained by NCTU.

Whilst it will not be possible to blind parents to the treatment allocation, efforts will be made to minimise expectation bias by emphasising that knowledge of whether using emollient in addition to best practice infant skin care advice, is currently limited.

Where possible researchers will remain blinded throughout the trial - the only face to face contact with the parents will be prior to the child being born and at 24 months. Since the skin examination is one year after the advice to stop using emollient, the blinding will not be affected by which group the child was in which might otherwise have been compromised at a one year examination by the moisturised appearance of the baby's skin and emollient tubs around the house. Additionally, parents will be asked **not** to discuss with the researcher how they cared for their child's skin over the first year.

Once participants have been randomised into the main trial they will be further randomised to a sub-study that will investigate two different interventions designed to maximise collection of follow up data in the trial. Allocation will be stratified by BEEP main trial arm (advice to apply emollient or control arm) and will be concealed by using an online randomisation system provided by NCTU.

Maintenance of randomisation codes and procedures for breaking code

Only the parents and the NCTU trial team will be aware of the allocation. Since the intervention is advice to use daily emollient, no special arrangements are necessary for the breaking of the randomisation code. All researchers will be asked to record unblinding at the 24 months visit which will be used to inform a sensitivity analysis.

TRIAL MANAGEMENT

The trial is funded by the NIHR Health Technology Assessment Programme. It is sponsored by the University of Nottingham, and will be managed and co-ordinated from NCTU.

The Trial Steering Committee (TSC) will meet at least once a year and will provide overall supervision of the trial on behalf of the trial sponsor.

The Trial Management Group (TMG) will meet more frequently and will be responsible for the day-to-day management of the trial. Members of the TMG will report to the TSC at their meetings.

Due to the very low medical risk associated with the advice to use daily emollient for the first year in addition to best practice infant skin care advice, no data monitoring committee (DMC) will be required as their function will be covered by the TSC. The Statistical Analysis Plan SAP) will be signed off by an independent statistician who will sit on the TSC.

The Chief Investigator has overall responsibility for the trial, shall oversee all trial management and will be the data custodian.

DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

Duration of the Trial

The duration of the trial is 8 years (96 months). There will be a 6 month set-up stage, two year (24 months) recruitment period with five year (60 month) follow up period for data collection. There will finally be 6 months allotted for data analysis. The timelines will be monitored throughout the trial and adjusted as necessary to reflect the progress of the trial.

Duration of Participant Involvement

Each participant will take part in this trial for five years (from randomisation) with the primary outcome at the 24 month time point. The primary outcome will be analysed and reported once all 24 month data are collected, keeping participants identity and information protected.

End of the Trial

The end of the full trial will be receipt of the final expected 60 month questionnaire to NCTU.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

We will look to publicise the study to expectant mothers and fathers in many different ways. In the main, parents will approach the study team if they are interested after seeing some publicity about the study, but a member of their care team may also mention the study to parents. Therefore recruitment into this trial will come from a variety of sources, including primary and secondary care and advertising.

Primary Care: In some areas large GP surgeries may be used as sites. In other areas where secondary care hospitals are the main site, GP surgeries will be used as Patient Identification Centres, whereby invitation letters and information sheets will be sent to potential participants. Invitation letters may be sent via Docmail®, if this is routinely used in the practice, in order to ensure mail outs are managed efficiently. Posters and flyers may also be put on display at participating GP surgeries. Midwives and Health Visitors will also be engaged to promote the study through posters, fliers, and word of mouth in clinics.

Secondary care centres will be used to advertise the study through the display of posters and leaflets (though not limited to) in antenatal clinics and hospital corridors. Participants may also be identified through antenatal and secondary care clinics in which case relevant health care professionals may approach parents directly about the study, or send invitation letters.

If identified through secondary or primary care the initial approach will be from a member of the patient's usual care team (which may include the investigator), and information about the trial will be on display in the relevant clinical areas.

Direct local advertising (radio, television, newspapers) and the public display of posters and fliers at venues that families and expectant mothers frequent (child centres, libraries, baby fairs etc.) will also be used. Online advertising or articles will promote the study and its website on (though not inclusive of) parent focused websites and forums, eczema websites

and forums, and emails to distribution lists of parents who have consented previously to being contacted about paediatric eczema research.

For most recruitment methods, it will be at the discretion of the expectant mother/parent of the new-born to contact the research team directly if they are interested in taking part. Interested families can contact local researchers, the general beep study email address (beep@nottingham.ac.uk) or get more information from the beep study website (www.beepstudy.org). The investigator at each research site or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant and their parent/legal guardian of all aspects pertaining to participation in the study.

Due to the long duration of the trial, efforts will be made to ensure the trial team continue to have up to date contact details for participants. Parents will be asked on each questionnaire to inform us of any change to their contact details and NCTU will securely store any other contact details given (i.e. emollient delivery address) and used in the event of being unable to contact the participant. If this attempt to gain contact fails the researcher will contact the GP to investigate further.

The participant information sheets, consent forms and all other study documentation will only be available in English; therefore all consenting parents must understand English language to be able to consent to this trial.

It will be explained to the potential participant (parent) that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

- Child has a first degree relative with parental reported doctor diagnosis of eczema, allergic rhinitis 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 to this trial. If multiple birth the first child will be randomised into the trial.
- Child has a 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.

Removal of participants from therapy or assessments

Children may be withdrawn from the trial at any time by their parents. Parents will be made aware that withdrawing from the trial will not affect the future care of themselves or their child, but that the data already collected cannot be erased and will still be used in the final

analysis. The primary reasons for discontinuation/withdrawal will be asked and recorded if the parent wishes to provide it.

Whilst parents may decide to not follow the advice provided, this is not grounds for withdrawal from the trial and encouragement will be given for the parent to continue to complete questionnaires and meet with the researcher at 24 months.

Participants who are withdrawn after randomisation will not be replaced.

Screening

When parents make initial contact with the study team, they will be given a brief explanation about the study. If they express an interest in taking part, they will be asked about family history of atopy and pregnancy status to check they are eligible. The full participant information leaflet will then be sent to the parents and a face to face screening visit arranged with the researcher, either in the family home, or at the hospital (depending on parental preference). This initial contact and basic eligibility screening may be done by either telephone or email, depending on how the parents choose to contact the study team, or face to face if the study is mentioned to the parents by a member of the care team e.g. midwives or dermatologists. If the initial approach is made during pregnancy then screening will be arranged usually for during the third trimester. However, if parents find out about the study after delivery then the screening visit will be done as soon as possible but definitely within 21 days of delivery. During the screening visit, informed consent will be obtained and pre-delivery eligibility assessed. Where the screening visit takes place during pregnancy, the researcher will also provide information about how to contact him/her when her child is born

Informed consent

Where consent is obtained **before the child is born** the mother must provide the written informed consent. The consent form will be signed and dated before entering the trial. A member of the research team will explain the details of the trial and provide a Participant Information Sheet, ensuring that the mother has sufficient time to consider participating. A member of the research team will answer any questions that the mother has concerning trial participation. In this scenario, a verbal check for continuing consent will be made at the telephone contact after the birth of the child prior to randomisation.

Where informed consent is obtained **after the birth**, either the mother or father can give consent but it must take place within 21 days of the birth of the child.

One copy of the consent form will be kept by the consenting parent, one will be kept by the Investigator, and a third will be sent to the child's GP.

Informed consent will be obtained for the provision of a saliva sample from the child (for genetic testing), and the parents will be offered the possibility of opting out of this part of the trial if they wish. In line with current guidance the mother will not receive their child's filaggrin test results (46).

Should there be any subsequent amendment to the final protocol, which might affect participation in the trial, continuing consent will be obtained using an amended consent form.

TRIAL TREATMENT AND REGIMEN

Interventions

The parent/child pair will be randomised to receive either best practice infant skin care advice or this same best practice infant skin care advice with the additional advice to apply emollient at least once a day from birth until age of one (intervention group).

Both groups will be given advice on best practice skin care in two formats; a booklet sent in the post and a web link to a video clip. This will contain information on avoiding soap etc. The advice given to the emollient (intervention) group will also explain how to apply the emollient i.e. in the direction of the hair all over their child's skin daily for the first year of life.

At randomisation, the intervention group will be sent both emollients to choose from (Doublebase Gel® and Diprobase Cream®). Parents will be asked to re-order their preferred emollient from central supplies throughout the intervention period as required. Details of which emollient, the date and quantity of emollient supplied will be recorded by the pharmacy and sent to NCTU to maintain blinding of researcher.

A saliva sample will be taken from the baby, by the researcher, at the 24 month visit for those who have consented to the optional genetic test. This will be obtained by the child spitting in a pot or a swab being taken from inside their cheek with a cotton bud.

There is planned sub-study for this trial where everyone taking part will be randomised to two interventions designed to maximise data collection. Firstly this will involve half of the participants receiving a text message reminder that the questionnaires are ready to be completed and other half not receiving the text message reminder. Secondly half the participants will be compensated *before* completion of the 24 month questionnaire with a voucher and the other half receiving the voucher *after* completion of the 24 month questionnaire. If during the study it is clear that one of the sub study interventions has a very positive affect, this may then be applied throughout the rest of the trial to maximise data collection.

Data collection methods

Flow chart 1: The research process involved for the participant – Pg 23.
Table 1: The summary of trial assessments – Pg 24.

Baseline and randomisation

Randomisation will take place within 21 days of the birth of the baby and this will be considered the baseline for this study. The researcher will check that the baby has been delivered safely, that all post-delivery eligibility criteria are met (either by phone or email with the family), and carry out the randomisation via the web-based randomisation system. The research team at the NCTU will then notify the family of their allocated group and arrange for shipment of the skin care advice (and emollient where appropriate), the EQ-5D-5L questionnaire, and will also provide via email the web link to the skin care video. The researcher will not be informed of the treatment allocation in order to maintain blinding for the primary outcome assessment.

Initial follow up

Approximately two weeks after randomisation the NCTU will contact parents to check they have received their skin care advice pack and web link, and to check the date that the family started applying the emollient, where appropriate. Parents will be reminded to contact the NCTU in future if they have any questions or problems (to protect the researcher from becoming unblinded).

Follow up (months 0-24)

Parents will be followed up by questionnaire at 3, 6, 12, and 18 months. These questionnaires will be completed online by most parents, and an email containing a web-link will be sent to alert parents that the questionnaire is ready to complete. Where families have no internet access, paper copies of the questionnaires will be provided by post with pre-paid envelopes for return. Parents will be further randomly allocated to either receive a SMS notification that the questionnaires are ready to be completed or not. All children will also receive a birthday card in the post from the BEEP Study Team on their first birthday.

The questionnaires will include questions on eczema and other allergy symptoms, diagnosis, treatment and health resource use, feeding, skin care practices, skin infections and infant slippage incidents within an hour of applying the skin care products, as detailed in table 1.
For logistical reasons, the parental health related quality of life (EQ-5D-5L) will not be completed online and instead it will be sent with the skin care advice at baseline with a pre-paid envelope for return. Where there is a parent reported doctor diagnosis of eczema, the POEM eczema severity scale will also be completed at 12 months. At 24 months all parents will be asked to complete a POEM regardless of doctor diagnosis of eczema. Where questionnaires are not completed or returned, a reminder will be sent by email or post after 2 and 4 weeks of non-completion. If contact is lost but parents have not withdrawn their consent, we will contact the GP to find out of the family contact details have changed and also collect data on eczema diagnosis at 24 months.

At 24 months, there will be a face to face visit with the researcher either in the family home or at the hospital (depending on parental preference). At this visit, the researcher will conduct a blinded examination of the child's skin for signs of eczema for the primary outcome, complete the EASI eczema severity scale, take a saliva sample for the genetic study (where consent has been given) and ask the 24 months set of questions This will involve the parents being asked to complete the IDQoL (if the child meets diagnostic criteria for eczema), the EQ-5D-5L, PedsQL and a detailed questionnaire about food allergy symptoms in their child.

Long term follow-up (36, 48 and 60 months)

Parents will continue to be sent questionnaires (either online or by post as before) at 36, 48 and 60 months to capture long term outcomes (eczema and other allergy symptoms, diagnosis, treatment, health resource use and quality of life).

Compliance

Adherence with the advice to apply emollient will be assessed using the 3, 6 and 12 month questionnaires.

Parents in the emollient group will be asked how often they apply the emollient; where on the child emollient was applied; how many times a day it was applied and why emollient has not been used (if that is indeed the case). Parents in the control group will be asked if they have regularly used any creams or oils on their child's skin (excluding nappy rash etc.), if so, what they used, how often and where on the child's skin.

Wide spread emollient use over the majority of the child's body at least three or more days per week will be considered as compliant in the intervention group and as contamination in the control group.

Criteria for terminating trial

This trial involves providing skin care advice to all parents with the intervention group receiving additional advice to apply emollient daily to their child for the first year. The emollients available are considered to be very low risk and as such, the chance of adverse effects as a result of emollient use is very small. Data on skin infections and slippages due to skin products will be collected to inform any decision on possible trial termination.

The chief investigator may stop the trial or terminate a recruiting centre if new information becomes available causing major safety concerns, or if there are issues with trial conduct.

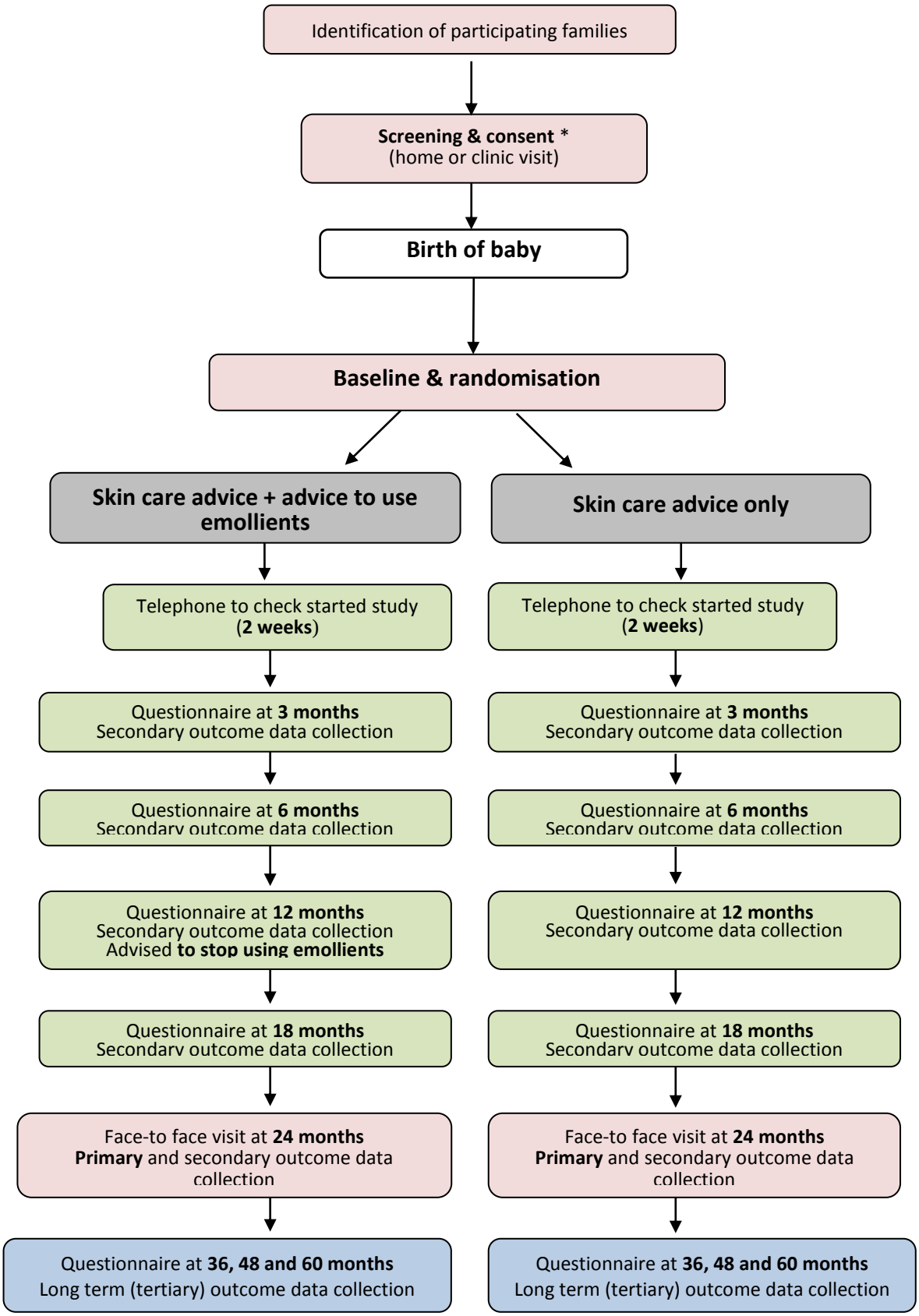
FILAGGRIN GENETICS ANALYSES

Saliva samples will be collected via the child spitting into a pot or swabs taken from the inside of the child's cheek at the 24 month visit, providing consent has been gained. The containers will be sent to the Centre for Dermatology & Genetic Medicine, University of Dundee where DNA will be extracted by standard techniques and *FLG* genotyping for the most prevalent null-alleles according to published protocols (47) with the addition of recent, unpublished protocol optimisations. Samples will be securely stored within the University of Dundee until testing takes place. If consent is given to this optional extra, any remaining samples will be stored for testing other genes found to be associated with eczema in the future.

Although every effort will be made to obtain a sample at the time of the 24 month visit, if this is not possible, a sample kit will be sent through the post to the parents with a self-addressed prepaid envelope to return directly to the laboratory.

Sample containers will be identified using the designated participant ID number and date of birth only. Personal contact details will be kept by the trial team and will not be transferred to the laboratory researchers. *FLG* genotype status will be recorded and returned to the NCTU using the unique participant ID and date of birth.

Flow Chart 1: Participant process



*** Screening can take place either during pregnancy or within 21 days of delivery**

Table 1 – Table of assessments

	Screening [1]	Baseline [2]	2 Weeks (+/- 1 week)	3 months	6 months	12 months	18 months	24 months (+/- 1 month)[3]	36, 48, 60 months
Confirm eligibility	X	X							
Informed consent	X								
Demographic data	X	X							
Randomisation		X							
Send skin care package (& emollient)		X							
Check parents received skin care package etc. and collect start date			X						
Parent reported skin problems (including eczema)				X	X	X	X	X	X
Parental completion of eczema diagnostic criteria (UK working party criteria)						X		X	X
Blinded assessment of eczema status by researcher								X	
Eczema severity, parental reported (POEM)						X		X	X
Eczema severity, blinded assessment by researcher (EASI)								X	
Adverse events (skin infections & slippages only)				X	X	X			
Emollient use				X	X	X			
Feeding practices					X				
Probiotic use					X				
Washing / bathing practices					X	X		X	
Hayfever / allergic rhinitis symptoms and diagnosis								X	X[4]
Wheezing / asthma symptoms and diagnosis								X	X
Food allergy symptoms and diagnosis						X		X	X
Health related quality of life (EQ-5D-5L, PedsQL and IDQoL)		X[5]						X	X[6]
Health service utilisation				X	X	X	X	X	X
Collection of saliva sample								X	

[1] The face-to-face screening visit can take place either during pregnancy or within the first 21 days after the birth of the child. If taking pace after birth, the screening and baseline visit may be combined providing sufficient time is given to allow parents to properly consider the study.

[2] Baseline (randomisation) must take place within 21 days of the birth of the child.

[3] The 24 month face-to-face visit from researcher where a blinded examination of the child skin will take place [4] Hayfever clinical diagnosis at 60 months only

[5] Only EQ-5D-5L to be completed
[6] Only PedsQL to be completed only where there is a doctor diagnosis of eczema

STATISTICS

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.

The assumptions underpinning the sample size will be checked by independent members of the TSC/DMC after approximately 21 months of recruitment, when approximately 75 children will have reached the 18 month follow-up time point in each group. The total sample size for the study and recruitment period may be increased at this point.

Methods

Appropriate descriptive statistics will be used to compare the two groups at baseline. The main approach to all analyses will be to analyse participants as randomised (intention-to-treat), regardless of adherence with allocation and without imputation for missing data. All analyses will be carried out using Stata/SE 13 or above.

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. Analyses of the long term outcomes will then be performed.

The primary outcome (proportion of children with eczema between 1 and 2 years of age) will be analysed using a generalised linear model adjusting for stratification variables used in the randomisation procedure. The difference between the two groups will be summarised using a relative risk (with a value of less than 1 indicating a reduction in eczema in the group receiving additional advice to use emollient) with 95% confidence interval. This will be the primary, confirmatory analysis. Sensitivity analyses will be performed on the primary outcome as follows:

- Using multiple imputation for missing outcomes
- Including any prognostic variables showing a baseline imbalance (based on examination only) in the model, and
- Taking account of the actual emollient use in the two groups

These analyses will be considered supportive to the primary outcome.

Analyses of secondary and long term outcomes will use appropriate regression models depending on the type of outcome. Differences between the two groups will be summarised with 95% confidence intervals.

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. Categorisation of emollient use will be performed prior to database lock and blinded to randomised group and the occurrence of safety events.

Descriptive information will also be provided on the frequency of possible eczema prevention practices post randomisation to explore if there are any differences according to group to inform the interpretation of the results.

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. Therefore, the baseline characteristics of these participants in the two groups will be compared informally and any characteristics with an obvious imbalance included in the regression models.

Planned subgroup analyses according to none/one or more FLG null mutations, the number of immediate family members with atopic disease and the number of immediate family members with eczema will be conducted by including an interaction term in the regression analysis for the primary outcome.

More details of the planned analyses, including the retention sub-study, will be documented in a Statistical Analysis Plan (SAP). The planned analyses of the primary, secondary and safety outcomes will be finalised prior to unblinding of the trial when data collection for the primary outcome at 2 years of age has been completed.

COST EFFECTIVENESS ANALYSIS

Objective

To estimate the cost effectiveness of the intervention from an NHS perspective in the short term (2 years within trial analysis) and, if appropriate, longer term (model-based analysis).
All resource use will be captured as detailed elsewhere in this protocol.

A range of outcome measures will be used in the economic evaluation to address different questions and to reflect the fact that there is no consensus over how to measure children's utility (Ungar, 2010). We will use:

a) Number of eczema cases prevented at 24 months.
b) Infant's Dermatitis Quality of Life Index (IDQOL) proxy completed by the parent for children with eczema at 24 months. IDQOL has previously been used in economic evaluations and is designed for children <4 years of age.
c) PedsQL proxy completed by the parent for all participating children at 24, 36, 48 and 60 months.
d) EQ-5D-5L self-completed by the parent to assess parental health-related quality of life (HRQL) at baseline and 24 months.

Within trial analysis: only patient-specific data collected within the 24 months period will be used. The incremental cost per eczema case prevented, incremental cost per one point less improvement in IDQOL, incremental cost per QALY based on PedsQL (parental-proxy reported), and incremental cost per QALY based on parents' own health related Quality of life(EQ-5D-5L) will be estimated. An incremental cost-effectiveness analysis will be performed using accepted methods (Drummond et al 2005) with data reported in a disaggregated way. Analysis of uncertainty will follow recommended practice (with results presented as cost-effectiveness acceptability curves).

Longer term model-based analysis: If the provision of additional advice to use emollient daily for the first year of life is found effective at 2 years, a longer term economic model will be developed to model the economic costs and benefits of the intervention for a single birth cohort from birth to 16 years, this time frame is appropriate as the majority of children do not enter adulthood with eczema although up to 50% may have recurrences in adulthood. Using trial data, within-trial cost effectiveness analysis and data collected in the 36-60 months follow-up period, in addition to other published data, expert opinion and population datasets (as appropriate), a decision analytic model taking an NHS perspective will be developed to assess the costs and benefits of the additional advice to use emollient in the first year of life compared to no such advice. This framework provides a systematic approach to decision making under uncertainty by incorporating the likely probabilities, costs and outcomes.

ADVERSE EVENTS

This trial poses very little risk to participants since it is comparing two skin care advice packages using emollients that are widely used. Adverse events that could be influenced by the trial interventions are being collected as outcomes for the trial, rather than AEs or SAEs. For this reason the AEs and SAEs will not be routinely collected for this trial. The two safety endpoints are:

1. The number of skin infections that the child experiences in the first 12 months (determined via the parental completed questionnaires).
2. The number of slippages (limited to the infant) in the first 12 months of the trial within an hour of applying emollient. This will be asked on the questionnaires. The number of these slippage incidents is anticipated to be very low (based on the pilot study) so the likelihood of a relationship to emollient use will be determined by further contact with the family triggered by a positive response to the question.

The development or worsening of eczema will not be considered an adverse event and information about this will be collected and derived as specific end points.

Participant removal from the trial due to adverse events

Any child who is advised to not follow the trial skin care advice will be encouraged to remain in the trial to complete follow-up questionnaires and to meet the researcher at 24 months.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval/favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining parent informed consent will be in accordance with the REC guidance, Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the parent shall both sign and date the informed consent form before the person can participate in the trial.

The decision regarding participation in the trial is entirely voluntary. The investigator or their nominee shall emphasize to the parent that consent regarding trial participation may be withdrawn at any time without penalty or affecting the quality or quantity of their child's future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be carried out before informed consent has been obtained.

The investigator will inform the parent of any relevant information that becomes available during the course of the trial, and will discuss with them, whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).

CRFs will be treated as confidential documents and held securely in a password protected location in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, contact details, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.
Access to the CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigators and recorded on the 'Trial Delegation Log.'

All paper forms shall be completed and collected in line with GCP. The local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling

Each participant will be assigned a unique trial identity code number at randomisation for use on the samples, consent forms and other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).

The University of Dundee will not receive any other participant details (samples will be linked anonymised, with only researchers at the UoN having access to the study recruitment log).

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results / records and electronic questionnaires. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below. All paper questionnaires will be stored securely in locked office in a locked cabinet at NCTU.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room in a locked cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. A member of the trial team, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

During the period of the trial, press releases and other publicity material may be issued from NCTU or the Centre of Evidence Based Dermatology, or collaborating centres as needed (in collaboration with the co-ordinating centre).

Trial related publications and conference presentations will be submitted to the NIHR HTA for approval prior to submission to the event organisers or the editors. All publications will acknowledge the support of the NIHR HTA in funding this trial.

We will send all participating families a summary of the trial results.
Neutral or negative results will not constitute a reasonable justification to delay publication.

USER AND PUBLIC INVOLVEMENT

Parents have been involved with the development of this trial through participation in a pilot study in which all participating parents were asked for their opinions on the pilot trial and proposed differences between the pilot and this main RCT. Additionally, a panel of parents has been drawn from parents who took part in the pilot trial to advise further on the trial design and associated documentation. We will invite at least one member of the panel to participate in the trial oversight committee.

TRIAL FINANCES

Funding source

This trial is funded by NIHR Health Technology Assessment (reference 12/67/12)

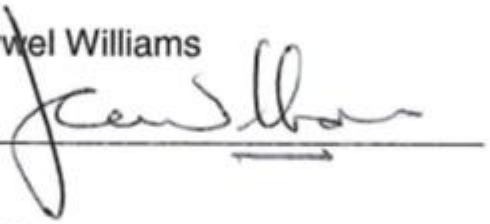
Participant stipends and payments

Participating families will receive no monetary payment for taking part in this trial. Travel expenses will be offered for any clinic visits that are primarily for the purpose of the trial. Vouchers of £10 value and low value gifts appropriate to the trial will be offered to encourage continued completion of questionnaires.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Hywel Williams

Signature: 

Date: 2nd Oct 2014

Trial Statistician: Lucy Bradshaw

Signature: Lucy Bradshaw

Date: 2nd Oct 2014.

REFERENCES

1. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. The Journal of allergy and clinical immunology. 2004 May;113(5):832-6. PubMed PMID: 15131563. Epub 2004/05/08. eng.
2. Malik G, Tagiyeva N, Aucott L, McNeill G, Turner SW. Changing trends in asthma in 9-12 year olds between 1964 and 2009. Archives of disease in childhood. 2011 Mar;96(3):227-31. PubMed PMID: 21068081. Epub 2010/11/12. eng.
3. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. The Journal of allergy and clinical immunology. 2009 Dec;124(6):1251-8 e23. PubMed PMID: 20004783. Epub 2009/12/17. eng.
4. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? The Journal of allergy and clinical immunology. 2008 Apr;121(4):947-54 e15. PubMed PMID: 18155278. Epub 2007/12/25. eng.
5. Williams HC, Wuthrich B. The natural history of atopic dermatitis. In: Williams HC, editor. Atopic Dermatitis. Cambridge: Cambridge University Press. p. 41-59
6. Tang TS, Bieber T, Williams HC. Does "autoreactivity" play a role in atopic dermatitis? The Journal of allergy and clinical immunology. 2012 May;129(5):1209-15 e2. PubMed PMID: 22409986. Epub 2012/03/14. eng.
7. Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. Allergy. 2010 Dec;65(12):1506-24. PubMed PMID: 20716320. Epub 2010/08/19. eng.
8. Kemp AS. Cost of illness of atopic dermatitis in children: a societal perspective. PharmacoEconomics. 2003;21(2):105-13. PubMed PMID: 12515572. Epub 2003/01/08. eng.
9. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, et al. The Global Burden of Skin Disease in 2010: An Analysis of the Prevalence and Impact of Skin Conditions. The Journal of investigative dermatology. 2013 Oct 28. PubMed PMID: 24166134. Epub 2013/10/30. Eng.
10. Jenner N, Campbell J, Marks R. Morbidity and cost of atopic eczema in Australia. The Australasian journal of dermatology. 2004 Feb;45(1):16-22. PubMed PMID: 14961903. Epub 2004/02/14. eng.
11. Verboom P, Hakkaart-Van L, Sturkenboom M, De Zeeuw R, Menke H, Rutten F. The cost of atopic dermatitis in the Netherlands: an international comparison. The British journal of dermatology. 2002 Oct;147(4):716-24. PubMed PMID: 12366418. Epub 2002/10/09. eng.
12. Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. Pediatric dermatology. 2008 Jan-Feb;25(1):1-6. PubMed PMID: 18304144. Epub 2008/02/29. eng.
13. Kerr OA, Tidman MJ, Walker JJ, Aldridge RD, Benton EC. The profile of dermatological problems in primary care. Clinical and experimental dermatology. 2010 Jun;35(4):380-3. PubMed PMID: 19874334. Epub 2009/10/31. eng.
14. NICE. NICE guideline: Management of atopic eczema in children from birth up to the age of 12 years. 2007. Available from: http://guidance.nice.org.uk/CG57/Guidance/pdf/English
15. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2004 Apr;34(4):520-6. PubMed PMID: 15080802. Epub 2004/04/15. eng.

16. Punekar YS, Sheikh A. Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2009 Dec;39(12):1889-95. PubMed PMID: 19817751. Epub 2009/10/13. eng.
17. Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. Allergy, asthma & immunology research. 2011 Apr;3(2):67-73. PubMed PMID: 21461244. Pubmed Central PMCID: PMC3062798. Epub 2011/04/05. eng.
18. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. The Journal of allergy and clinical immunology. 2007 Sep;120(3):565-9. PubMed PMID: 17655920. Epub 2007/07/28. eng.
19. von Kobyletzki LB, Bornehag CG, Hasselgren M, Larsson M, Lindstrom CB, Svensson A. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. BMC dermatology. 2012;12:11. PubMed PMID: 22839963. Pubmed Central PMCID: PMC3469362. Epub 2012/07/31. eng.
20. Austin JB, Kaur B, Anderson HR, Burr M, Harkins LS, Strachan DP, et al. Hay fever, eczema, and wheeze: a nationwide UK study (ISAAC, international study of asthma and allergies in childhood). Archives of disease in childhood. 1999 Sep;81(3):225-30. PubMed PMID: 10451395. Pubmed Central PMCID: PMC1718047. Epub 1999/08/18. eng.
21. Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? BMJ (Clinical research ed). 1994 Apr 30;308(6937):1132-5. PubMed PMID: 8173454. Pubmed Central PMCID: PMC2540131. Epub 1994/04/30. eng.
22. Simpson CR, Newton J, Hippisley-Cox J, Sheikh A. Trends in the epidemiology and prescribing of medication for eczema in England. Journal of the Royal Society of Medicine. 2009 Mar;102(3):108-17. PubMed PMID: 19297652. Pubmed Central PMCID: PMC2746851. Epub 2009/03/20. eng.
23. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? The British journal of dermatology. 2005 Feb;152(2):202-16. PubMed PMID: 15727630. Epub 2005/02/25. eng.
24. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. Current problems in dermatology. 2011;41:1-34. PubMed PMID: 21576944. Epub 2011/05/18. eng.
25. Brown SJ, McLean WH. Eczema genetics: current state of knowledge and future goals. The Journal of investigative dermatology. 2009 Mar;129(3):543-52. PubMed PMID: 19209157. Epub 2009/02/12. eng.
26. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nature genetics. 2006 Apr;38(4):441-6. PubMed PMID: 16550169. Epub 2006/03/22. eng.
27. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. The New England journal of medicine. 2011 Oct 6;365(14):1315-27. PubMed PMID: 21991953. Epub 2011/10/14. eng.
28. Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. The Journal of allergy and clinical immunology. 2009 Jun;123(6):1361-70 e7. PubMed PMID: 19501237. Epub 2009/06/09. eng.
29. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. The Journal of allergy and clinical immunology. 2008 Apr;121(4):872-7 e9. PubMed PMID: 18325573. Epub 2008/03/08. eng.
30. Brown SJ, Relton CL, Liao H, Zhao Y, Sandilands A, Wilson IJ, et al. Filaggrin null mutations and childhood atopic eczema: a population-based case-control study. The Journal of allergy and clinical immunology. 2008 Apr;121(4):940-46 e3. PubMed PMID: 18313126. Epub 2008/03/04. eng.

31. Uehara M, Miyauchi H. The morphologic characteristics of dry skin in atopic dermatitis. Archives of dermatology. 1984 Sep;120(9):1186-90. PubMed PMID: 6476856. Epub 1984/09/01. eng.
32. Flohr C. Atopic dermatitis diagnostic criteria and outcome measures for clinical trials: still a mess. The Journal of investigative dermatology. 2011 Mar;131(3):557-9. PubMed PMID: 21307951. Epub 2011/02/11. eng.
33. Cork MJ, Danby S. Aqueous cream damages the skin barrier. The British journal of dermatology. 2011 Jun;164(6):1179-80. PubMed PMID: 21615367. Epub 2011/05/28. eng.
34. Hachem JP, Houben E, Crumrine D, Man MQ, Schurer N, Roelandt T, et al. Serine protease signaling of epidermal permeability barrier homeostasis. The Journal of investigative dermatology. 2006 Sep;126(9):2074-86. PubMed PMID: 16691196. Epub 2006/05/13. eng.
35. Cork MJ. The importance of skin barrier function. Journal of Dermatological Treatment. 1997; 8(1 , Pages S7-S13):S7-S13
36. Nakajima S, Igyarto BZ, Honda T, Egawa G, Otsuka A, Hara-Chikuma M, et al. Langerhans cells are critical in epicutaneous sensitization with protein antigen via thymic stromal lymphopoietin receptor signaling. The Journal of allergy and clinical immunology. 2012 Apr;129(4):1048-55 e6. PubMed PMID: 22385635. Epub 2012/03/06. eng.
37. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. The New England journal of medicine. 2003 Mar 13;348(11):977-85. PubMed PMID: 12637607. Epub 2003/03/15. eng.
38. Williams C, Wilkinson SM, McShane P, Lewis J, Pennington D, Pierce S, et al. A double-blind, randomized study to assess the effectiveness of different moisturizers in preventing dermatitis induced by hand washing to simulate healthcare use. The British journal of dermatology. 2010 May;162(5):1088-92. PubMed PMID: 20199550. Epub 2010/03/05. eng.
39. Edwards WH, Conner JM, Soll RF. The effect of prophylactic ointment therapy on nosocomial sepsis rates and skin integrity in infants with birth weights of 501 to 1000 g. Pediatrics. 2004 May;113(5):1195-203. PubMed PMID: 15121929. Epub 2004/05/04. eng.
40. Wiren K, Nohlgard C, Nyberg F, Holm L, Svensson M, Johannesson A, et al. Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial. Journal of the European Academy of Dermatology and Venereology : JEADV. 2009 Nov;23(11):1267-72. PubMed PMID: 19508310. Epub 2009/06/11. eng.
41. Batchelor JM, Ridd MJ, Clarke T, Ahmed A, Cox M, Crowe S, et al. The Eczema Priority Setting Partnership: a collaboration between patients, carers, clinicians and researchers to identify and prioritize important research questions for the treatment of eczema. The British journal of dermatology. 2013 Mar;168(3):577-82. PubMed PMID: 22963149. Epub 2012/09/12. eng.
42. Macharia WM, Anabwani GM, Owili DM. Effects of skin contactants on evolution of atopic dermatitis in children: a case control study. Tropical doctor. 1991 Jul;21(3):104-6. PubMed PMID: 1926547. Epub 1991/07/01. eng.
43. Darmstadt GL, Saha SK, Ahmed AS, Ahmed S, Chowdhury MA, Law PA, et al. Effect of skin barrier therapy on neonatal mortality rates in preterm infants in Bangladesh: a randomized, controlled, clinical trial. Pediatrics. 2008 Mar;121(3):522-9. PubMed PMID: 18310201. Epub 2008/03/04. eng.
44. Kataoka Y, Yoshida N, Nishino H, N. M, Sarumaru T, Kimjima A, et al. Can skin care from neonatal period prevent the onset of atopic dermatitis? Allergo J. 2010;19 (P5):7.
45. Simpson EL, Berry TM, Brown PA, Hanifin JM. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. Journal of the American Academy of Dermatology. 2010 Oct;63(4):587-93. PubMed PMID: WOS:000282069400005.
46. Fabsitz RR, McGuire A, Sharp RR, Puggal M, Beskow LM, Biesecker LG, et al. Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute working group. Circulation

Cardiovascular genetics. 2010 Dec;3(6):574-80. PubMed PMID: 21156933. Pubmed Central PMCID: 3090664. Epub 2010/12/16. eng.
47. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nature genetics. 2007 May;39(5):650-4. PubMed PMID: 17417636. Epub 2007/04/10. eng.

APPENDIX 1

The UK refinement of the Hanifin and Rajka diagnostic criteria for atopic eczema

An itchy skin condition in the last 12 months

Plus three or more of:

i. Onset below age 2*
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