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

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Short title: Barrier Enhancement for Eczema Prevention

Acronym: BEEP

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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 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 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, food allergy, allergic sensitization, 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
CHU-9D	Child Health Utility – Nine Dimensions
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
NHS	National Health Service
NCTU	Nottingham Clinical Trials Unit
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
SPT	Skin Prick Test
TMG	Trial Management Group
TSC	Trial Steering Committee

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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 food allergy and 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 Recent work has shown a strong dose-response relationship between eczema during infancy and risk of food allergy, and a recent systematic review found evidence that eczema may directly cause food allergy(18, 19). Population-based cohort studies also reveal a relationship between eczema and other allergenic diseases around one in three children with eczema go on to develop asthma, especially allergic asthma (20). 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 (21). Around half of UK school children with eczema also suffer from allergic rhinitis (22).

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 (23), 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, 24). 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 (25, 26). 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 (27), common mutations in the gene encoding filaggrin, a key skin barrier protein, represent the strongest known genetic risk factor for eczema (28, 29). 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 (30). Approximately 40% of moderate or severe eczema cases in hospital practice carry one or more filaggrin loss-of-function mutations (31, 32).

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 and food allergy, 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 (33). 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, 34), 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 (35). 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 (35-37). 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 (33) 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 (38). In support of this, there is increasing evidence that eczema during infancy may directly cause food allergy(19).

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 (32) and that peanut oil on the skin during childhood may be a predictor of confirmed peanut allergy (39), 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 (40). Emollients have been shown in premature babies to reduce the incidence of skin inflammation (41), to reduce flares of eczema (secondary prevention) and to decrease the need for topical steroids (42). 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 (43). 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 (44), 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 (45). 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 (46). 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% (47). 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. However this study has now been terminated prior to any participants being enrolled into the trial.

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) (48).

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 risk of food allergy.
    - The risk of allergic sensitisation to food or non-food allergens.
    - The risk of onset of other allergic diseases (asthma and allergic rhinitis).
- 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 maximum of 1400 participants will be recruited over a 24 month period with five year follow up and primary outcome assessed at two years.

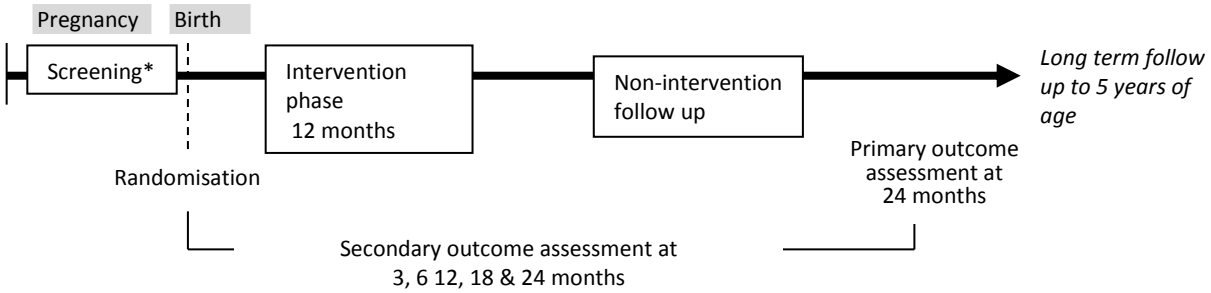
Screening will take place either during pregnancy or soon after delivery during a face-to-face visit with the researcher. Families will be randomised within 21 days of delivery of their baby to one of two groups in a 1:1 ratio:

- **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 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.
6. 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.
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. 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.

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.

All outcomes relating to food allergy and food sensitization are funded by a grant from Sheffield Children's Hospital Charity.

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.

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 (49).

Informed consent will be obtained for an optional allergy test (skin prick test) at the time of the 24 month assessment. A separate Participant Information Sheet and consent form will be used for this optional outcome assessment. The information sheet will be sent to participants before the 24 month assessment. The consent form will be signed and dated by a parent or guardian on the day of the assessment, before allergy testing is performed.

Based on the responses given in questionnaires together with the results of the allergy test the child may be invited to have an optional food challenge. A modified form of the algorithm used

in the EAT study will be used to select participants for invitation to a food challenge (50). Those invited to a food challenge will receive a separate Participant Information Sheet at the time of invitation, and will sign a separate consent form on the day of the food challenge.

For all consent forms one copy 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.

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 follow-up with a voucher and the other half receiving the voucher *after* completion of the 24 month follow-up. 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

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.
Parents who have not completed the questionnaires will be given the opportunity to complete the questionnaires over the phone with the trial coordinating centre. It will be documented which method of questionnaire completion was used.

All children will also receive a birthday card in the post from the BEEP Study Team on every birthday up to the age of five.

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/GP surgery (depending on parental preference). The visit will be made at a time that is convenient for the participant as per usual site practice for booking appointments. Confirmation of the 24 month visit will be sent to the participant. 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 and perform a Skin Prick Test (where consent has been given for these two optional sets of tests) and ask the 24 months set of questions This will involve the parents being asked to complete the EQ-5D-5L (in order to measure parental health-related quality of life), CHU-9D and a detailed questionnaire including questions about food allergy symptoms in their child. The child's GP will be notified by letter from the site that the 24 month visit has taken place.

As at baseline parents consent to relevant sections of their child's medical notes being consulted and used for the purposes of the study, an abridged version of the 24 month visit case report form will be sent to the GP of children that are not seen by a nurse for a 24 month visit.

Food Allergy Testing

The process around the food allergy testing is outlined in a flowchart on page 28 of the protocol.

Skin Prick Testing: At the 24 month visit an optional allergic sensitisation test will be carried out using the skin prick technique in order to determine an essential part of the diagnosis of food allergy. Parents are sent the information sheet about the skin prick test from the study nurse included with the letter confirming their 24 month visit appointment time. During the 24 month visit nurses will review the allergy testing PIS with the parents/guardians and give them the opportunity to consent to this additional testing. Skin prick testing has been carried out in the community and in the home in several other large paediatric studies both in the UK (51-53) and internationally (54, 55).

Allergens tested will be food allergens (milk, egg and peanut) and non-food allergens (cat, grass pollen and house dust mite). This testing will be carried out following a trial-specific procedure (see Appendix 2) for skin prick testing, in line with the British Society for Allergy and Clinical Immunology paediatric skin prick testing standard operating procedure(56). Nurses will be trained by allergy specialists in using the rescue medications referenced within these guidelines (cetirizine and auto adrenaline injectors), and they will be available for use at each appointment. The likelihood of needing either rescue medication is very low as systemic reactions to skin prick tests are extremely rare (57, 58). Even in cases where an allergy does exist, the most likely reaction to a skin prick test is an itchy sensation at the test site. Systemic reactions (ie a reaction beyond the site of the test) such as itchy skin/eyes/mouth, hives, coughing, have an occurrence rate of 1 in 10,000 for a skin prick test(59), and the likelihood of a serious allergic reaction requiring use of an auto adrenaline injector is estimated at 1 in 1 million (59, 60).

Food Challenge: Participants with a positive SPT or history suggestive of food allergy, where allergy diagnosis needs further confirmation, may be invited for a supervised oral food challenge. If necessary, the parent will be contacted by members of the trial team following their skin prick test to be given more information about the food challenge and may also be asked further questions about the child's food allergy history. A trial specific food challenge information sheet will also be sent to parents of children invited to the food challenge. If a parent wishes for their child to participate in a food challenge they will be scheduled in to undergo a supervised food challenge in an allergy clinic at Imperial College Healthcare NHS Trust and Sheffield Children's Hospital Trust, in order to confirm or refute the diagnosis of food allergy in the child. If travel distance proves to be too great for many families, it is possible that food challenges may be arranged in allergy clinics at other study sites.

Standard procedures will be used for the food challenge (see Appendix 3) – incremental or doses or a single dose of the relevant food will be given in a hospital setting, and trained experiencednurses supported by a consultant paediatric allergist will evaluate whether there has been a clinical reaction to the food using modified PRACTALL criteria(61). Food challenge assessors will remain blind to treatment allocation of participants, and where feasible, to skin prick test results, although this may not be possible where participants request a skin prick test on the day of the food challenge. Clinical reactions during food challenge will be treated using standard clinical guidelines, with antihistamine, bronchodilator, intramuscular adrenaline or other medications, as needed.

Results of the Skin Prick Test and the Food Challenge (where applicable) will be sent in a letter to the parent/guardian and the child's GP by the BEEP allergy researchers.

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

Parents will continue to be sent questionnaires (either online or by post as before, with the opportunity to complete over the phone) 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

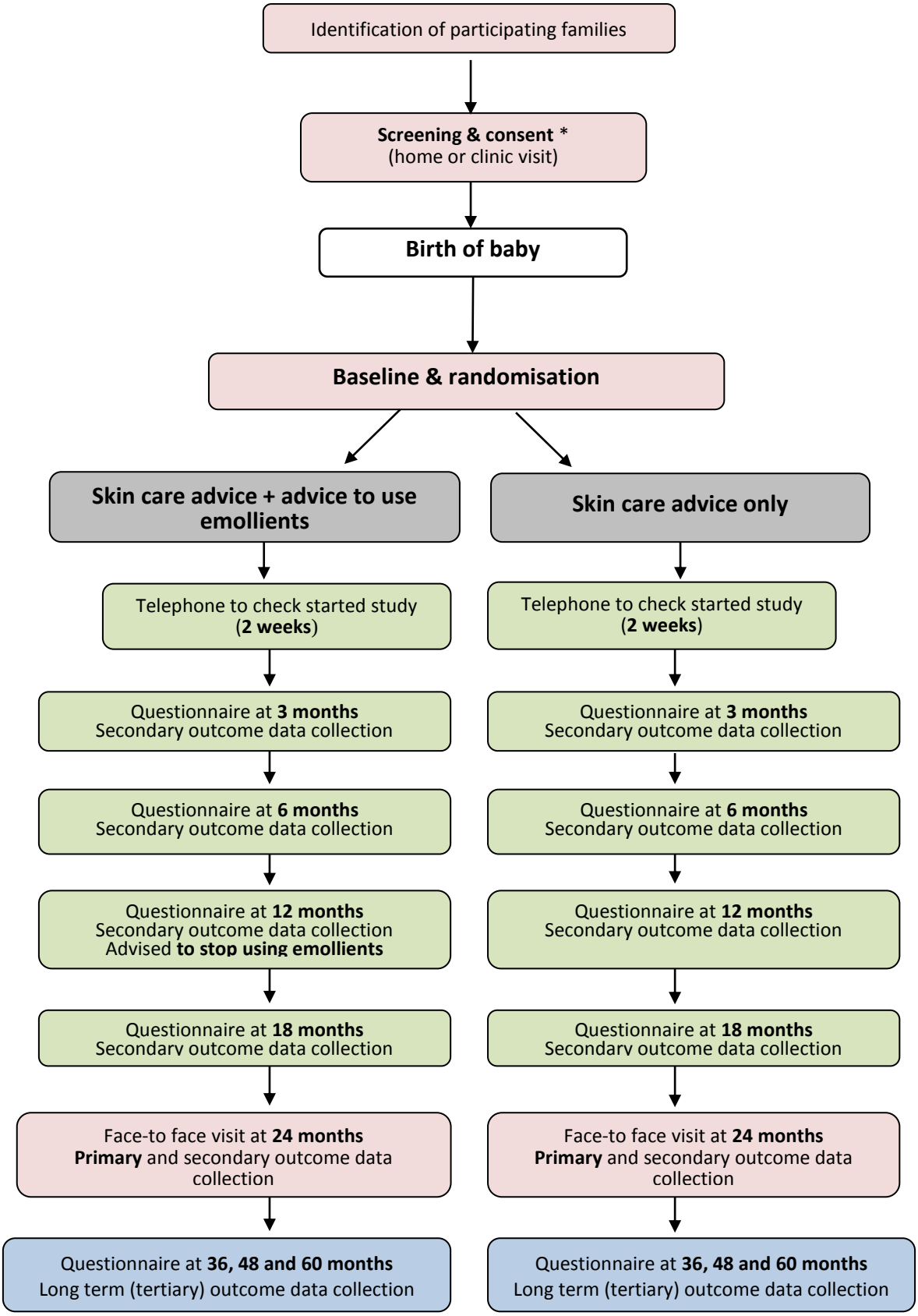
Saliva samples will be collected via the child spitting into a pot or swabs taken from the inside of the child's cheek at the 24 month visit, providing consent has been gained. The containers will be sent to the University of Dundee where DNA will be extracted by standard techniques and *FLG* genotyping for the most prevalent null-alleles according to published protocols (62) with the addition of recent, unpublished protocol optimisations. An online sample tracking system has been developed by the coordinating centre to track the sending of samples from sites to University of Dundee.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**

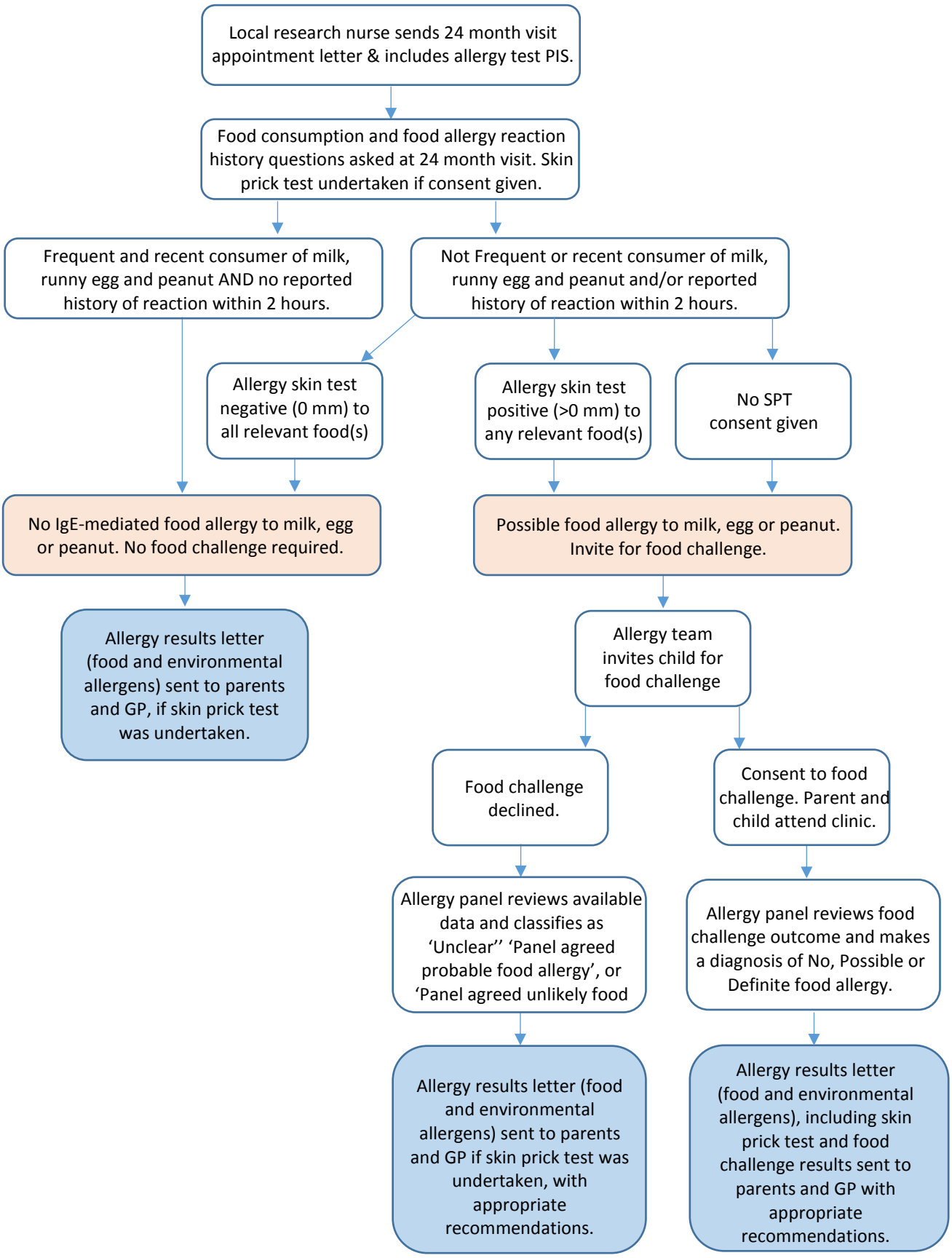
Table 1 – Table of assessments

	Screening [1]	**Baseline** [2]	**2 Weeks (+/- 1 week)**	**3 months**	**6 months**	**12 months**	**18 months**	**24 months (- 1, +2 months)[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
Skin Prick Test								X	
Food Challenge								After 24 month visit, if needed.	
Health related quality of life (EQ-5D-5L and CHU-9D)		X[5]						X	X
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. This visit can take place from 23 (-1) to 26 (+2) months post birth.
[4] Hayfever clinical diagnosis at 60 months only
[5] Only EQ-5D-5L to be completed

Flow chart 2: The process involved for food allergy assessments



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.

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 participants who had consented to the study who had not yet been randomised. Randomisation to the study will close on 19 November 2016 with up to 1400 participants randomised.

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 data collected from GP records for participants with missing outcome
- 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 two 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 and potential sensitivity analyses for the food allergy/sensitization outcomes, 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.

ECONOMIC EVALUATION

Objective

To estimate the cost effectiveness of the intervention from an NHS perspective in the short term (24 months within trial analysis), medium term (60 months within trial analysis) and, if appropriate, longer term (birth to 16 years using a model-based analysis). Intervention resource use will be recorded over the first 12 months. Disease related NHS resource use will be captured (as specified elsewhere in this protocol) at 3, 6, 12, 18, 36, 48 and 60 months and valued using published unit costs for the most recent price year available.

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 (63). We will use:

a) CHU-9D proxy completed by the parent for all participating children at 24, 36, 48 and 60 months(64).
b) EQ-5D-5L [www.euroqol.org] self-completed by the main parent to assess parental health-related quality of life (HRQL) at baseline and 24 , 36, 48 and 60 months.
c) Number of eczema cases prevented at 24 months.

Within trial analysis: For the within-trial analyses (both short and medium term), incremental cost per QALY based on CHU-9D (parental-proxy reported) (base case analysis), incremental cost per QALY based on parents' own health related Quality of life (EQ-5D-5L), and the incremental cost per eczema case prevented will be estimated. Incremental cost-effectiveness analyses will be performed using accepted methods (65-68)with data reported in a disaggregated

way. Analysis of uncertainty will follow recommended practice (with results presented as cost-effectiveness acceptability curves)(69, 70).

Longer term model-based analysis: If the provision of additional advice to use emollient daily for the first year of life is found to be significantly more effective than usual care at 24 months, 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, the within-trial cost effectiveness analyses, in addition to other published data, expert opinion and population datasets (as appropriate and available), 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.

Procedures for missing, unused and spurious data

Every effort will be made within the trial to minimise the occurrence of missing data. For the primary outcome at 24 months, nurses will make every effort to schedule a visit with the family. Where it is not possible to have a face to face visit (family move abroad, family unwilling) some key visit data may be collected by the nurse via other methods (e.g. telephone, text, email or post). Where a family may have moved to another region since time of randomisation, they will be followed-up by a nurse from a closer recruiting centre, if possible. In instances where the family is not contactable for the 24 month visit (e.g. withdrawal or lost to follow-up), the trial team will attempt to collect minimal key data from the participant's GP.

Methods to deal with missing data for the primary outcome are described in the statistical methods section.

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. Sites must complete a source data location log which lists where source data is found. This should be filed in the Investigator Site File, at site and at the coordinating centre. 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)

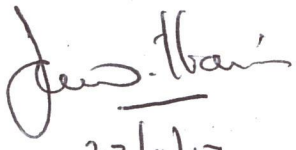
Participant stipends and payments

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. Travel and childcare expenses will be reimbursed to any family travelling to clinic to take part in a food challenge.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Hywel Williams

Signature: 

Date: 23/11/17

Trial Statistician: Lucy Bradshaw

Signature: Lucy Bradshaw

Date: 23 Nov 2017.

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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

APPENDIX 2: BEEP Trial Skin Prick Testing Working Practice Document

What is a Skin Prick Test: A Skin Prick Test (SPT) is a common allergy test whereby a tiny droplet of an allergen is placed on to the skin. In those who demonstrate an IgE mediated allergic response to the allergen, a small localised wheal and redness will form at the test site. The size of the wheal is then measured using a standardised ruler. The reaction can help to confirm an allergy, in combination with the patient's medical history. The test is both simple and safe, and results can be read within 15 minutes of administration.

Why are SPTs being done as a part of the BEEP Trial: Recent studies have shown that having eczema may increase the risk of developing other allergies, especially food allergy (1, 2, 3, 4). There are treatments for allergy, but we don't know how to prevent it. It is possible that skin care advice including the regular application of moisturiser from birth might prevent food allergy, and possibly other allergies, as well as preventing eczema. The best way to find this out is to do an allergy test for children in the BEEP study.

When will the SPT be done: BEEP Practitioners will perform a Skin Prick Test (where parental consent has been given) at the 24 month visit.

Where will the SPT take place: This will likely be done in the home environment, unless parental preference is to have the 24 month visit take place in the clinic.

Who can perform the Skin Prick Test: SPT should be performed by trained clinical BEEP practitioners (nurse, midwife, clinician) who must have the following qualifications and skills:
1) Trained in paediatric resuscitation*
2) Completed the 24 month visit training
3) Qualified to administer the emergency medications*
4) Signed off for proficiency in SPT by a BEEP Allergy nurse specialist or consultant

**if the individual is not qualified to administer emergency medications and/or trained in paediatric resuscitation, the visit must take place in a secondary care clinic setting where appropriate physician cover is immediately available.*

SPT Results: The BEEP practitioner will measure the reactions and record these in the BEEP CRF. Interpretation of these results will be made by the BEEP Allergy Team and the parent and GP of the child will be notified at a later date by post.

Equipment: All equipment will be supplied to the site by the BEEP Allergy Team. The following equipment is used for SPTs in the BEEP Trial:

- Allergen solutions:
  - From Allergopharma, Reinbeck, Germany
    - Positive Control 1% Histamine
    - Negative Control 0.9% Saline
    - Grass pollen mix
    - Dust mite
    - Cat
  - From Inmunotek, Madrid Spain
    - Peanut
  - To be bought fresh by local site each week:
    - Milk : Skimmed fresh cow's milk
    - Egg: Chicken egg
  - All allergens to be stored in a refrigerator when not in use.

- Lancets (manufacturer ALK, Horsholm, Denmark)
- Portable sharps bin
- Clean tissue for blotting the solutions
- Pen
- Timer/clock
- Skin test measuring ruler
- BEEP 24 month visit CRF workbook

Emergency equipment: procured by site nurses from their Trust
Auto Adrenaline Injector: EpiPen Junior (0.15mg) , 2 injectors
Sugar-free Cetirizine solution 5mg/5mls (200ml bottle)

Procedure:	
1.	Correctly identify the patient
2.	Explain the procedure to the child/family. Obtain written consent.
3.	Check with the parent that the child has not taken any anti-histamines for two days prior to the test and that the child is well with no fever or acute wheeze
4.	Have the necessary equipment (listed above) available. Check the manufacturer's expiry date on all solutions and equipment.
5.	Perform correct hand washing prior to procedure
6.	Ensure the child is sitting comfortably, ideally placed on their parent's/guardian's lap and arrange suitable distraction (e.g. video on a portable device or TV). A pillow or cushion may be used to rest the child's arm on.
7.	Select an appropriate area of skin for the test on the child's forearm. The test should only be performed on clear eczema free skin. If the arm is not clear, the back can be used.
8.	On skin where topical steroids or other creams have been applied, the skin can be gently washed with warm water then patted dry before undertaking the skin prick test. The site chosen should not be cleaned with antiseptics or alcohol.
9.	Mark the skin with 8 letters or numbers for the 8 allergy tests – negative and positive controls and fresh milk, raw egg, peanut, cat, house dust mite and grass pollen. The tests should ideally be a minimum of 2 cm apart and 5cm above the distal crease of the wrist. Both forearms can be used if necessary.
10.	Start the procedure by placing one drop of the negative control in line with their marked places on the skin, then repeat the process for the requested other allergens, ending with the positive control (Histamine), milk and egg white
11.	A fresh sterile lancet should be inserted through each drop into the superficial layer of the skin at a 90 degree angle. Sufficient pressure should be applied to make a small visible hole in the skin, but not enough to cause bleeding. The procedure is virtually painless, and it can be helpful to show the parent/guardian on their own forearm first for reassurance
12.	The lancet should then be immediately discarded into the sharps bin
13.	Repeat the procedure for each allergen and the controls using a new lancet for each new allergen or control

14.	Start a timer and carefully remove the surplus fluid from each site using a clean piece of tissue. Be careful to avoid contaminating one drop with another
15.	The test sites may become itchy, but the child should avoid scratching for 15 minutes. Blowing on the forearm, or placing a cold flannel over the test site can help reduce itching
16.	During the 15 minute wait, continue on with asking the parents the further questions in the CRF workbook or having them complete the paper questionnaires.
17.	At 15 minutes, examine each wheal and document the size in the BEEP 24 month visit CRF workbook using the validated SPT ruler you have been given. For negative results a '0' should be written and for positive results the widest part of the wheal should be measured in millimetres plus the diameter at 90 degrees to the widest one
18.	Document the results in the BEEP 24 month visit CRF workbook. If participants have questions about the results, remind them that they will receive a letter summarising the findings and any recommended action in the post, which is also sent to their GP

Emergency Procedures, to be undertaken as per usual clinical care, especially:	
Anaphylaxis	• Follow Allergy Action Plan • Immediately Administer the Epipen Junior (0.15mg). • Call 999. The child will need to be taken to hospital. • Monitor child until they are in emergency care • Complete details of reaction in BEEP 24 month CRF.
Mild to moderate allergic response (itchy skin, eyes, mouth; hives; coughing)	• Follow Allergy Action Plan • Oral administration of one 5mg dose of Cetirizine. • Monitor symptoms until stable. • Complete details of reaction in BEEP 24 month CRF.

References:

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APPENDIX 3: BEEP Trial Oral Food Challenge Working Practice Document

Step 1: Perform Clinical Assessment

On the day of the challenge, participating children will be assessed by the attending BEEP study nurse or physician to determine their suitability for a food challenge using the checklist on the CRF. This includes ensuring that the child has no acute exacerbation of allergic signs or symptoms, or intercurrent febrile illness, which may mask symptoms during a food challenge; and ensuring that emergency drugs and equipment detailed below are in place, in date and readily available.

Where a child did not previously have a skin prick test at their 24 month visit, the parent may request to have it done on the day prior to the food challenge. If the skin prick test results are negative for the challenge food, the food challenge will not need to take place.

Allergy box contents include:
EpiPen 0.15mg x 2
Cetirizine 5mg/5ml 200mls
Chlorphenamine 10mg vial
Salbutamol 100mcg metered dose inhaler
Salbutamol 2.5mg nebules
Adrenaline 1:1000 5mg/5ml for nebulising
Adrenaline 1:1000 (1mg/ml) for adrenaline injection/infusion
Prednisolone soluble tablets 5mg
Hydrocortisone for IV/IM injection 100mg

Equipment which needs to be available:
Volumatic spacer, nebulising mask, high flow oxygen mask, 0.9%saline 500ml bag for rapid infusion, 0.9% saline 100ml bag and syringe driver for adrenaline infusion, saline 0.9% 10ml vials, water for injection 10ml vials

The assessing nurse/physician must take all steps to ensure that they do not become aware of participant's treatment allocation in BEEP i.e. emollient versus standard care. They may review skin prick test results and allergy history as needed to inform clinical decision making. Episodes of unblinding to treatment allocation should be recorded on the food challenge CRF.

Prior to commencing the food challenge, baseline observations including temperature, heart rate, respiratory rate, oxygen saturation and findings on auscultation of the chest should be documented on the CRF.

High risk challenges. Where an allergic reaction is felt to be likely, or potentially severe, the study nurse/physician should consider inserting an intravenous cannula and informing the Paediatric Intensive Care Unit, prior to commencing the food challenge. Where this is planned or considered, the case should always be discussed with the supervising doctor. Examples where this might be considered are: participants with high level sensitisation on skin prick testing, and no previous exposure to the food; participants with known allergy to the food and a history of previous severe reaction (i.e. a reaction accompanied by hypoxia, hypotension, and loss of consciousness or admission to intensive care).

Step 2: Food Challenge Procedure

Administer five doses of allergenic food protein of 0.03, 0.1, 0.3, 1 and 3 g in separate portions at 30 minute intervals. Total dose 4.33g protein. Doses for milk, egg and peanut are shown in the Table below. For high risk challenges additional initial low doses may be included, at the supervising doctor's discretion. For low risk challenges the complete 4.33g protein may be given as a single dose, at the supervising doctor's discretion.

Table 1. BEEP food challenge dosing schedules

Food	g protein/100g	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
Peanut Butter	25	0.1g	0.4g	1.2g	4g	12g
Defatted Peanut Flour	50	0.06g	0.2g	0.6g	2g	6g
Cow's Milk	3.2g/100mls	0.9ml	3ml	9ml	30ml	90ml
Raw Egg White	11g	0.3g*	0.9g	2.7g	9g	27g

*1ml raw egg white weighs 1g.

Allergenic Food Sources:
Fresh whole cow's milk, Red Lion salmonella-free eggs, Sunpat peanut butter (or defatted, lightly roasted peanut flour from the Golden Peanut company, if peanut butter is not tolerated).

For participants who are reluctant to ingest the food challenge doses, they can be mixed with Nesquik flavouring (Cow's Milk), yoghurt or fruit puree/sauce (Raw Egg White; Defatted Peanut Flour), mashed banana or other fruit puree (Peanut Butter).

Doses are given at 30 minute intervals. Where there is concern about possible allergic symptoms (e.g. orange symptoms below), doses may be delayed by increasing the dosing interval to 60 minutes, or repeating the last dose.

Step 3: Recording symptoms during food challenge
Record all symptoms which are of new onset and not due to ongoing disease, and occur within two hours of a food challenge dose using the trial-specific record chart that contains guidance for stopping food challenges. Stopping a food challenge and treating symptoms are always at the local clinical team's discretion. The UK Resuscitation Council algorithm for managing severe allergic reactions (Anaphylaxis) should be followed.

Step 4: After all challenge doses have been given, or the challenge has been stopped
If the result is negative: Observe child until at least 2 hours after the last dose was fully ingested

- Advise the family to give their child the challenge food again at home
- Telephone family 24-72 hours later to ask about any delayed symptoms
- Enter final outcome in CRF.

If the result is positive: Observe child until at least 1 hour after symptoms have settled, and only after they have had something more to eat. Children may be kept for longer according to the supervising doctor's discretion, and may be admitted to hospital for overnight observation if appropriate.

- Advise the family that the child must avoid the allergenic food in the diet.
- Provide a detailed written emergency management plan.
- Provide education on avoidance strategies.
- Provide training in EpiPen administration if indicated.
- Review the child's inhaler technique if appropriate.
- Encourage the parents to join the UK Anaphylaxis Campaign and Medic-Alert.