Nottingham University Hospitals NHS Trust

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Feasibility Study of Barrier Enhancement for Eczema Prevention (BEEP)

Protocol

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Acronym:	Barrier Enhancement for Eczema Prevention (BEEP)
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SYNOPSIS

Title	Feasibility Study of Barrier Enhancement for Eczema Prevention
Acronym	Barrier Enhancement for Eczema Prevention (BEEP)
Chief Investigator	Professor Hywel C. Williams
Objectives	To determine the feasibility of conducting a subsequent definitive randomised controlled trial which will investigate whether emollients used from birth can prevent eczema in high-risk babies.
Trial Configuration	Multi-centre randomised controlled parallel group trial.
Setting	This trial will recruit newborn babies at high-risk of developing eczema. A number of recruitment strategies will be tested in this feasibility trial including primary care, secondary care, antenatal care and advertising.
Sample size estimate	Approximately 40% families screened will have a history of atopy that predispose to a high risk of eczema in their offspring. Around 250 families will need to be approached in order to identify around 100 families (40%) at high risk of giving birth to a child with atopic disease.
Number of participants	100 families will be screened with approximately 40-60% of families expected to be randomised.
Eligibility criteria	**Inclusion criteria** • Participant (i.e. the newborn child) must have a parent or sibling with a history of at least one of the following: eczema, allergic rhinitis or asthma • Infant in overall good health • Mother at least 16 years of age at delivery • Capable of giving informed consent **Exclusion criteria** • Mother taken any pro-biotic supplements containing Lactobacillus rhamosus during pregnancy, or plans to take any whilst breastfeeding • Preterm birth defined as birth prior to 37 weeks gestation • Major congenital anomaly • Hydrops fetalis • Significant inflammatory skin disease at birth not including seborrheic dermatitis (“cradle cap”) • Any immunodeficiency disorder or severe genetic skin disorder • Any other serious condition that would make the use of emollients inadvisable. • Any other major medical problems that the investigator deems may increase the risk of adverse events with the intervention

Description of interventions	The intervention group will use emollients, from a choice of three types, at least once a day starting within 3 weeks of birth. The control group will not use emollients. Both groups will be given standardised best practice skin care advice which includes avoiding the use of soap.
Duration of study	Recruitment is planned to commence in February 2010 and should take approximately 6 months. Each family will participate in the study for 6 months. Families will be sent a questionnaire when the child is 1 and 2 years old to check whether they have developed any skin problems subsequent to their involvement in the study.
Randomisation and blinding	Participating families will be randomly allocated using a web-based computer generated internet randomisation service to either the intervention or the control group. Allocations will only be released once eligible participants' details have been irrevocably entered into an online database. The interventions (intensive barrier enhancement or normal care) are impossible to blind from trial participants. The main outcome assessor will be blinded to allocation status.
Outcome measures	The primary outcome measure will be the proportion of families willing to be randomised. This is the most critical component of the success of any future trial examining the effectiveness of this strategy for eczema prevention. The secondary outcomes are designed to further facilitate the design of a larger, controlled international multi-centre trial. • Proportion of families eligible for the trial • Proportion of families accepting the initial invitation to participateProportion of families who found the interventions acceptable • Reported adherence with intervention • Proportion of families for whom the blinding of the assessor to the allocation status was not compromised • Amount of contamination as a result of increased awareness in the control group. • Percentage of missing data and early withdrawal rates • Incidence of emollient-related adverse events • Incidence of eczema at 6 months, 12 months and 24 months. • Age at onset of eczema • Filaggrin gene mutation status
Statistical methods	One hundred families will provide a sufficiently precise (within 10 percentage points for a 95% confidence interval) estimate of the proportion willing to be randomized, assuming between 40 and 60% are willing to be randomised. The remaining outcome measures will then be assessed in those that are randomised. The intervention group will be treated as one pooled group regardless of which of the three emollients they used. The results will be judged against pre-determined success criteria that will indicate whether the feasibility study should proceed to a larger RCT.

ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BEEP	Barrier Enhancement for Eczema Prevention
CI	Chief Investigator
CRF	Case Report Forms
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
Filaggrin	Filament aggregating protein
GP	General Practitioner
HTA	Health Technology Assessment
ICH GCP	International Conference on Harmonisation Good Clinical Practice
Ig	Immunoglobulin
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TEWL	Trans-epidermal water loss
UK CRN	UK Clinical Research Network

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STUDY BACKGROUND INFORMATION AND RATIONALE

BACKGROUND

Eczema Prevention Studies

Previous eczema prevention strategies were based upon the notion that early life allergen exposures initiate childhood eczema. Maternal dietary antigens are indeed able to cross the placenta and have been found in breast milk.[1,2] Because the majority of eczema develops prior to the age of two,[3] interventions must begin *in utero* or in early infancy. Previous allergy-based eczema prevention strategies can be broadly characterized into maternal dietary manipulation, dietary manipulation of the infant, environmental allergen avoidance, and probiotic supplementation. Despite decades of research, however, no one allergy-based strategy has been proven consistently effective for the prevention of eczema.[4-6] These strategies are summarized below.

Maternal dietary restriction in pregnancy and lactation

The most recently published study evaluating maternal dietary restriction during *pregnancy* was published in 1999 and found no protective effect of a maternal exclusion diet on the development of eczema.[7] Previous work in this area has shown mixed results. A Cochrane review updated in 2006 found diet restriction during pregnancy may in fact negatively affect the nutritional status of the mother and fetus.[8] Dietary restriction during *lactation* may be a more promising approach, with three studies showing a protective effect.[9-11] Several published reviews on this subject, however, have tempered enthusiasm for these findings, citing the several methodological shortcomings found in these reports such as poor disease definitions.[5,8,12] In addition, three other studies have not shown favourable results.[13-15]

Dietary manipulation of the infant

Although there are several conflicting observational studies, some showing breastfeeding increases the risk of eczema,[16,17] all published reviews on the subject recommend breastfeeding for the first four months if possible to reduce the incidence of eczema in high-risk infants and to receive the numerous other health benefits.[12,18] Due to its weak and inconsistent protective effect, however, breastfeeding alone does not constitute an effective eczema prevention measure for the general population.

In the Cochrane review by Osborn published in 2006,[19] the authors concluded that there was “limited evidence” that hydrolyzed formulas protect against eczema in high-risk infants who cannot be breastfed. They pointed out the inconsistent results in previous studies (several studies have not found a protective effect [20,21]) and identify methodological concerns. They recommended larger, better designed studies. Since that report, the large, well-designed German Infant Nutritional Intervention Study (GINI) found modest protective effects up to six years of age for the use of partially hydrolyzed whey formulas and extensively hydrolyzed casein formulas.[22] Paradoxically, extensively hydrolyzed whey formulas were not protective. The American Academy of Pediatrics review from 2008

concluded that there is “modest evidence” that eczema may be delayed or prevented by the use of partially or extensively hydrolyzed formulas, compared to cow’s milk formulas.[12] The high cost and poor palatability of extensively hydrolyzed formulas, combined with their modest protective effects, make this approach expensive and impractical for large populations.

Environmental allergen avoidance

Although Hide reported that a combined approach of house dust mite reduction measures and dietary restriction imparted protection against the development of eczema,[23] house dust mite allergens are not likely to play a significant role in the development of eczema. A recent carefully planned prospective cohort study found no association between dust mite concentrations in the home and the future development of eczema.[24] Consistent with these results, two recent large interventional studies, totalling over 1000 participants, failed to find any protective effect of early reduction of house dust mite allergen on the future development of eczema.[25,26]

Probiotics

Probiotics are cultures of bacteria purported to colonize the digestive tract that exert beneficial health effects by unclear immunological mechanisms. The first report by Kalliomaki on the protective effect of probiotic supplementation was met with enthusiasm by the eczema research community despite some methodological deficiencies highlighted by Williams.[27,28] A meta-analysis published in 2007 of six studies confirmed a protective effect of maternal and infant probiotic supplementation on the development of eczema (OR 0.61, P<0.0001).[29] Since this review, three studies, including a replication study of Kalliomaki’s original report, have failed to show any protective effect of probiotic supplementation on the development of eczema.[30-32]

The Role of the Skin Barrier in Eczema Pathogenesis

The development of effective prevention strategies for eczema to date has been hampered, in part, by an unclear understanding of eczema pathogenesis. The pathogenesis of eczema is unknown, but two broad competing theories have emerged.[33] The first theory termed the “inside-out hypothesis” holds that defects in bone marrow-derived cells lead to immune overstimulation and subsequent skin inflammation. In support of this theory, numerous functional defects in eosinophils, basophils, monocytes and lymphocytes can be demonstrated from patients with eczema.[34] In addition, eczema can also be transferred or cured via bone marrow transplantation.[35] Lesional skin of patients with eczema reveal an abundance of infiltrating T lymphocytes, with acute lesions demonstrating a Th2-dominant cytokine profile.[36] The epidermal disruption observed in eczema lesions, according to this theory, is a consequence of cytokines and chemokines elaborated from skin-infiltrating T lymphocytes. The effect of Th2 cytokines on keratinocytes can largely explain several of the epidermal abnormalities observed in eczema. For example, Th2 cytokines have been shown to reduce epidermal lipid production, downregulate innate antimicrobial peptides, and reduce filaggrin expression thus impairing skin barrier function.[37-39]

The second theory, termed the “outside-in hypothesis,” states that defects in the epidermal skin barrier represents the primary defect in eczema. The inflammatory response develops

as a consequence of environmental allergens and irritants penetrating a defective skin barrier. Clinical evidence for skin barrier dysfunction in eczema include increased water permeability, decreased water content, increased susceptibility to skin irritants and chronic staphylococcal colonization within the stratum corneum of patients with eczema.[40-42] Enhanced serine protease activity has also been found in the skin of patients with eczema, which may contribute to epidermal disruption and promote inflammation.[43] Altered levels of stratum corneum lipids, particularly ceramides, have been consistently found in the lesional skin of patients with eczema, suggesting that defects in lipid biosynthesis may play an important role in the development of skin barrier dysfunction.[44-48] Replacing ceramides appears to correct the underlying skin barrier defect and leads to clinical improvement in skin inflammation (personal communication).[49,50] Recent basic research further supports the outside-in hypothesis and reveals that genetic defects in the skin barrier protein filaggrin may be an important trigger for the development of eczema.

The Role of Filaggrin Mutations in Eczema Development

In 2006, Palmer and colleagues reported that mutations in the skin barrier gene encoding filaggrin predispose individuals to the development of eczema.[51,52] These findings have been replicated over the past two years on an unprecedented scale with over 25 papers confirming these results in several European and Asian populations.[53,54] Several rare and prevalent mutations have been identified that lead to a functional absence of filaggrin protein, an essential component of a properly functioning epidermal barrier.[55]

The name of the protein (filaggrin) was derived from its function: filament aggregating protein. Specifically, it aggregates keratin filaments leading to a flattening of keratinocytes, in the process forming the stratum corneum. Filaggrin is further processed by proteolytic enzymes into amino acids that constitute the natural moisturizing factor that helps the stratum corneum retain water. In the absence of filaggrin, it is thought that keratinocytes are unable to appropriately flatten. Filaggrin is later cleaved to yield amino acids that form the so-called natural moisturizing factor (NMF). A truncated filaggrin protein yields a reduced amount of NMF and the stratum corneum becomes dehydrated and fissured. This leads to a dry and defective barrier that allows the influx of irritants and allergens leading to skin inflammation. The loss of filaggrin may also lead to a reduction in a filaggrin breakdown product, trans-urocanic acid, thus preventing proper acidification of the skin surface.[56] An elevated skin pH may promote stratum corneum serine protease activity and weaken its innate antimicrobial defense.

Although these data regarding filaggrin are compelling, recent population-based studies suggest other genetic or environmental factors are important for the full expression of the disease. Three population-based studies from Europe published in 2008, while confirming the association of filaggrin mutations with eczema, reveal the influence of filaggrin mutations on mild eczema is weaker than found in more severe populations.[57-59] The other genetic or environmental influences that alter risk for mild-moderate cases of eczema have yet to be identified, but researchers have suggested that infantile skin care may alter the risk for eczema development, especially in high-risk populations.[60,61]

Evidence That Early Childhood Skin Care May Modify Eczema Risk

The significant increase in eczema prevalence over the past 50 years in industrialized countries suggests environmental factors may play a role in the development of eczema.[62,63]

Environmental factors known to exacerbate established eczema include behaviours that erode the natural skin barrier such as hot water bathing, the use of soaps and detergents, and contact with wool and other irritants.[64] Mild soaps and even plain water have been shown to deteriorate the natural skin barrier in normal people.[65-67] Frequent bathing in neonates with a genetic predisposition to developing eczema may represent an important trigger for the disease. Cork correlated the rise in prevalence of eczema in the United Kingdom with the exponential rise in personal soap and detergent wash products.[68] Several authors suggest the excessive bathing and increased use of soap and detergents in the neonatal period initiates eczema in susceptible individuals.[60,61]

In contrast, a case-control study by Macharia did not find that the use of soaps or detergents in infancy increased the risk of eczema.[69] This was a small study performed over 15 years ago in Kenya, an area of the world with a low prevalence of eczema. This study did find a significant protective effect of the use of petrolatum in infancy on the future development of eczema (OR=0.33, P<0.05).

Surprisingly, no further studies have been performed that examine the effects of neonatal skin care practices on eczema development. In fact, there are very few studies examining the effects of various skin care methods on any aspect of newborn skin health. A systematic review by Walker in 2005 could not identify any previous studies examining the effects of skin care methods in newborns.[70] Work by the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) reached similar conclusions in their guidelines pertaining to neonatal skin care.[71]The National Institute for Health and Clinical Excellence could not identify any studies pertaining to bathing or skin care in the newborn when they formulated their educational booklet on postnatal care.[72] Studies are greatly needed to help establish recommendations for postnatal skin care for both the general population and in those at risk for eczema development.

Effect of Emollient Use on Skin Barrier Function

Studies in both healthy and diseased skin have shown that most oil-in-water emollients improve skin barrier function.[73-75] These positive effects of emollients on skin barrier function translate to improved clinical outcomes when emollients are used in the management of eczema. Emollients are first line therapy for the treatment of mild eczema and have a dramatic steroid sparing effect when added to the treatment regimen for patients with moderate to severe disease.[76]

Some emollient formulations, however, may have detrimental effects on the skin barrier. Held and colleagues showed a slight increase in irritant response in normal skin after treatment with an oil-in-water emollient, but no negative effect on Transepidermal water loss (TEWL) was seen.[77] Buraczewska and colleagues showed pre-treatment of normal skin with an emollient containing canola oil and urea worsened the skin barrier function after challenge with a skin irritant.[78] Water itself has also been shown to be a skin irritant making emollients high in water content (e.g. lotions) less appealing for eczema therapy.[66,67]

No single emollient formulation has proven superior in improving barrier function. Recent emollients have been formulated to mimic the natural chemical composition of the stratum corneum. Ceramides are important lipids needed for a functional skin barrier, and levels have been found to be reduced in the lesional skin of eczema. A ceramide-rich emollient was shown to be more effective in improving TEWL levels and clinical disease scores than routine emollients.[79] In contrast, a study by Loden and colleagues did not see a benefit of

skin-identical lipids over pure petrolatum in repairing the skin barrier after experimental perturbation.[80] A small pilot study in eczema prevention revealed that a simple petrolatum-based emollient is sufficient to maintain a normal skin barrier (personal communication). However it is not known whether emollients containing ceramides may be more effective at maintaining an adequate skin barrier.

Rationale for the Use of Emollients for Eczema Prevention

Despite the fact that emollients are considered first-line treatment for eczema in several published guidelines,[81-83] there are no previous studies examining early emollient use in the primary prevention of eczema. The first mention that emollient therapy may be an effective eczema prevention strategy first appeared in the literature in 2006. Recent advances elucidating the importance of the skin barrier in eczema now makes emollient therapy for eczema prevention a logical next step. There are five main lines of evidence to support the notion that emollient therapy from birth is likely to delay the onset or prevent the development of eczema. First, recent genetic and functional studies outlined above reveal that the skin barrier is a key factor in the development of eczema. Second, a small study by Kikuchi identified a trend towards decreased TEWL and skin hydration in participants prior to the development of eczema.[84] Third, a case-control study by Macharia found that the use of topical petrolatum in infancy significantly protected infants against eczema development.[69] Fourth, several studies in *premature* infants provide proof of principal that emollients may be utilized to prevent or delay the onset of skin inflammation. Seven studies have shown a reduction in the incidence of “dermatitis” or improved skin condition in premature neonates treated with emollients.[85-91]Lastly, the data from a pilot study (personal communication) strongly suggest a protective effect and demonstrate the preliminary safety of this approach in infants at-risk for eczema.

The mechanisms by which emollient therapy can prevent and treat skin inflammation are not fully known. Simple emollients such as petrolatum incorporate into the stratum corneum lamellar structure providing a barrier to allergens, irritants, and microbes that likely initiate inflammation.[92] Newer emollients may also maintain stratum corneum pH, thus reducing serine protease activation and subsequent barrier degradation.[93] Certain oils have also shown to reduce staphylococcus aureus colonization, an important driver of eczema inflammation.[94] Lastly, emollient therapy, in contrast to previous allergen avoidance strategies, has already been shown to reduce flares in eczema (secondary prevention).[76,95]

SIGNIFICANCE OF PROPOSED RESEARCH

The rising prevalence, patient morbidity, health care costs and potential toxicities of current therapies make disease modification and prevention in eczema an important goal. Quality research on the primary prevention of eczema is lacking. The Health Technology Assessment (HTA) review of treatments published in 2000 revealed only 7% of controlled trials on eczema treatment pertained to disease prevention and one of the six “urgent calls” was for the development of new eczema prevention strategies [5]

Barrier protection with emollients, although a cornerstone of eczema therapy, has not been previously explored as a disease prevention strategy. This strategy could be a cost-effective, easy and safe intervention to prevent or delay the onset of eczema. Finding an approach to even delay the onset of eczema or decrease its severity could have a large public health

impact. Results from the subsequent RCT will likely change the standard of care for neonates determined to be at risk for eczema. Future studies will include evaluating whether reducing the incidence and severity of eczema through skin barrier protection may positively impact the development of associated allergic diseases such as food allergy and asthma. Several lines of evidence suggest a defective skin barrier may lead to epicutaneous sensitization and the subsequent development of IgE-mediated diseases.[96,97] Improving the skin barrier may reduce epicutaneous sensitization and alter the risk for eczema -associated allergic diseases such as food allergy and asthma. Future studies will also expand in geographic scope and population number. Eczema is a global problem and the data generated from this proposal will facilitate larger studies on a more global scale.

TRIAL OBJECTIVE AND PURPOSE

HYPOTHESIS

Enhancing the skin barrier from birth using emollients will prevent or delay the onset of eczema in predisposed infants.

PURPOSE

The trial will NOT answer the question of whether emollient use will prevent or delay the onset of eczema – this will be the purpose of the subsequent definitive randomised controlled trial (RCT). Prior to undertaking such a large and expensive trial, information regarding the feasibility of this strategy is needed. Therefore, the purpose of this trial is to inform the design of the definitive RCT.

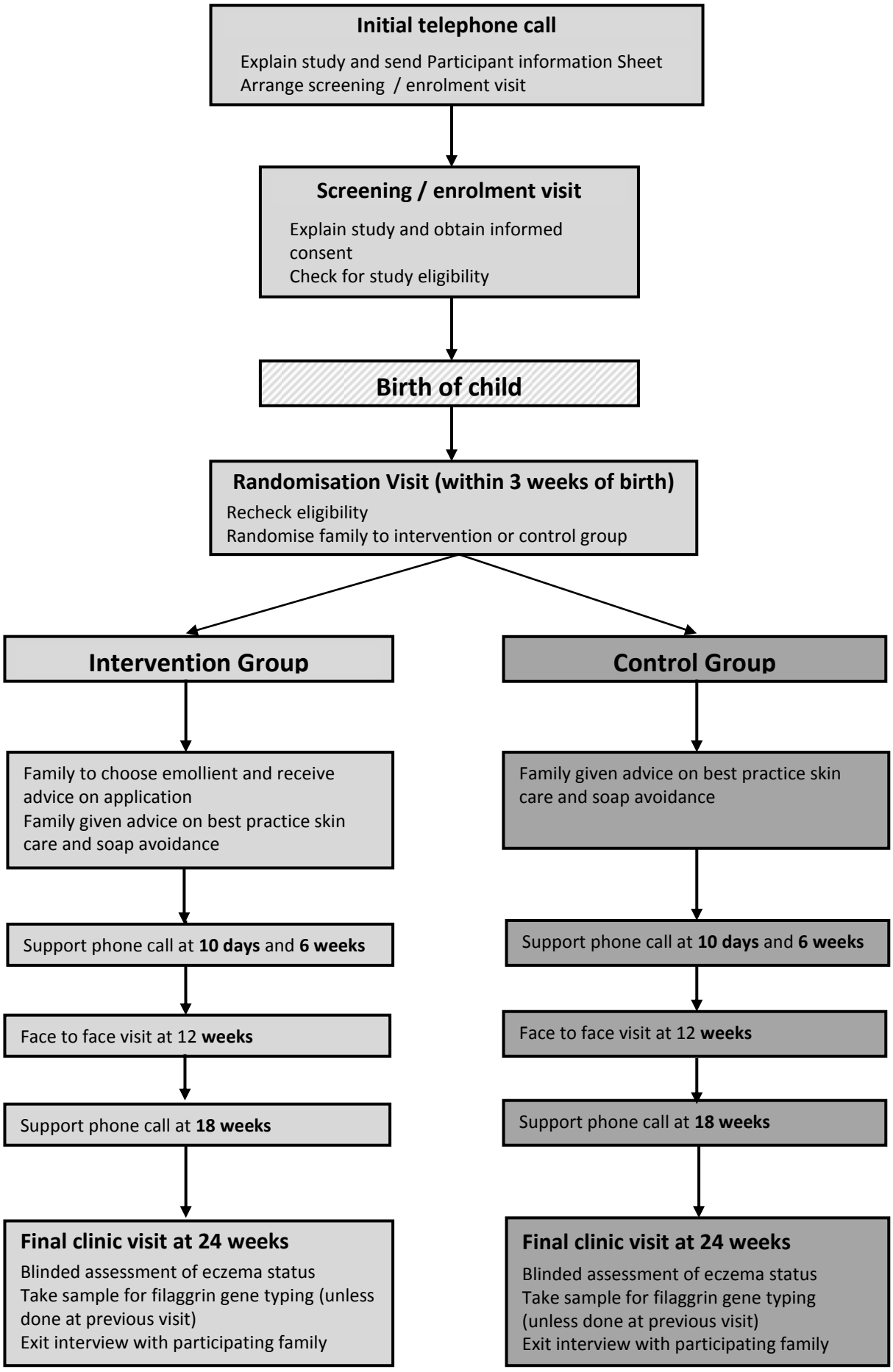
OBJECTIVE

To determine the feasibility of conducting a subsequent definitive randomised controlled trial which will investigate whether emollients used from birth can prevent eczema in high-risk babies.

TRIAL DESIGN

TRIAL CONFIGURATION

This is a multi-centre randomised controlled parallel group trial designed to establish the feasibility of conducting a large scale RCT. Families will be randomly allocated to the intervention (emollient) group or the non-intervention control group in a 1:1 ratio.



STUDY VISITS

Recruitment and identification of participants

This trial will recruit newborn babies at high-risk of developing eczema. Despite several studies attempting to identify cord blood markers, family history remains the strongest predictor of future eczema development.[5,104] Specifically, infants with a family history in one parent or sibling of allergic rhinitis, asthma, or eczema have an approximate 40% to 50% chance of developing eczema.[5]

A number of recruitment strategies will be tested in this feasibility study in order to determine the best method for the main RCT. These will include:

- Antenatal appointments including hospital clinics, midwives, health visitors and GPs
- GP practice database searches
- Dermatology and asthma clinics
- Publicity:
    - Newspapers, radio and TV
    - Posters in relevant hospital wards, GP surgeries
    - Relevant websites and organisations e.g. www.netmums.com, the National Childbirth Trust
    - Antenatal classes
    - Eczema support groups such as the National Eczema Society and the Nottingham Support Group for Carers of Children with Eczema.
    - Flyers in free gifts given out to pregnant women
    - Presenting to health professionals providing pre-natal care.

If other potential sources for recruitment become apparent during the trial, these will also be included.

If the family are identified as a result of their antenatal care e.g. via the midwives or GP database search, the initial approach letter will be from their normal care team. This will be sent from a member of the trial team prior to delivery, usually in the mother's last trimester of pregnancy. If the family is interested to find out more, they will return a reply slip or email the study team.

However, if the family become aware of the study as a result of advertising or publicity then they will make the initial approach directly to the study team.

Pre-trial

During the first contact with the study team, which is likely to be by telephone, an overview of the trial will be given and the requirement for a family history of atopic disease explained. After the initial discussion, if the family are interested, they will be sent a copy of the participant information leaflet and will consider their participation in the trial. If they would like to participate, an appointment for a screening / enrolment visit will be made. This may be a

separate appointment or combined with a normal antenatal care appointment if this is more convenient. If it is a separate visit, depending on the wishes of the family, the screening / enrolment visit will be conducted either at the family home or the hospital. This trial will test the feasibility of conducting visits in different ways to ascertain the best method for the subsequent RCT.

If the family do not wish to take part, they will be asked if they would be willing to share their reasons why. It will be explained that this is a feasibility study and that it is equally as important for the design of the main RCT to understand the reasons why people are not willing to take part.

Screening / enrolment visit

The screening / enrolment will usually take place during, or near to, the 3rd trimester of pregnancy. During the visit the family will be given ample opportunity to discuss the trial further with a member of the trial team and any questions they have will be answered. Informed consent will be obtained from one of the parents before undertaking any trial related procedures. Details of the family history of atopic diseases will be obtained and other pre-birth eligibility criteria will be checked. If the family meet the eligibility criteria, it will be explained that the research nurse will see them again after the baby is born so they can be randomised into the study.

The family will be asked to contact the study team once the baby is born so the randomisation visit can be arranged as soon as possible. Otherwise, a member of the study team will contact the family once the due date is reached.

Randomisation and Baseline Visit

The randomisation and baseline visit will take place as soon as possible after delivery (but within a maximum of 3 weeks). The eligibility criteria relating to the health status of the infant will be checked by a combination of discussion with the family and a check of medical records. If all criteria are met, then the family will be randomised into the study.

Families allocated to the intervention arm will be given standardised details of how to apply the emollients at least once a day (starting as soon as possible after birth) and how to record emollient usage. Samples of the emollients will be shown to the families so they can choose which emollient they would prefer to use. Families in both groups will receive standardised advice on general best practice skin care. This will include bathing, hair washing, avoiding lotions and wipes and use of a soap substitute. Any other aspects of skin care will be as per normal practice. Standard advice on allergy prevention will be provided.

If the family become aware of the study *after* the birth of the baby (for instance as a result of publicity on the post-natal ward), then the screening and randomisation visit will be conducted as one visit, providing it is still possible to start the study within 3 weeks of delivery.

Scheduled Interim Follow up Visits and Telephone Calls

Interim follow-up contact with the family is scheduled as follows:

- 10 days (telephone call)

- Week 6 (telephone call)
- Week 12 (face to face visit at home or clinic)
- Week 18 (telephone call)

These follow up visits will enable the trial team to answer any questions and address any areas of concern the families may have and provide support and reassurance for the participating families. General skin care of the infant will be reiterated and families will be asked specifically asked about any skin problems or adverse events the infant may currently have or had since the last contact.

For the intervention group only, the family will be asked about adherence to the emollient regimen and reminded about the correct use of emollients.

The 12 week face to face visit will be conducted either at the hospital or the family home, depending on the wishes of the family. A saliva sample will be taken either at this visit or the final visit at 24 weeks to test for filaggrin gene mutations. Alternatively, the research nurses will discuss with the family the option of doing the sample by post to allow the best collection method for the subsequent RCT to be determined. The research nurse will also examine the skin of the infant at this visit.

Final Trial Visit at 24 weeks

All families will have a final trial visit at 6 months. This is likely to be carried out at the hospital to enable the independent skin examination to be conducted. At this visit, the following trial procedures will be carried out:

- The infant will be clinically examined by an investigator (clinician or research nurse) who is blinded to the treatment allocation for the presence of eczema. This will be done primarily in order to test the feasibility of the blinding of the outcome assessor for the main RCT.
- They will also assess the infant for:
    - Presence or history of skin infection
    - ichthyosis vulgaris
    - keratosis pilaris
    - hyperlinear palms and soles
- A saliva sample will be taken to test for filaggrin gene mutations if this has not been done previously.
- Adherence to the emollient regimen will be assessed for those in the intervention group.
- Families will be asked for their opinion on their participation in the trial. This will be done by questionnaire and / or by semi-structured interview with a member of the trial team. Issues that will be addressed will include acceptability of the intervention, changes to skin care of the infant as a result of the trial, reasons for non-adherence and any suggestions of how the trial could be improved from a participant's perspective. All families will then be offered the opportunity to be contacted in the future to take part in further qualitative work planned which will support this feasibility study in the design of the main RCT.

Unscheduled visits

Participating families will be asked to contact the trial team for advice if the infant develops any dermatitis or other rash such as miliaria (heat rash), dry skin or skin infection at any point during the trial. If it persists for more than 7 days, then the family will be advised to attend the hospital for a trial visit. The infant will be assessed by an investigator who is blinded to the treatment allocation to see whether they have developed eczema or a skin infection. If the infant has a skin condition that requires treatment, they will be referred to their GP or an appropriate physician.

Withdrawal

If the family wish to withdraw early from the trial, they will be asked to attend for a final trial (withdrawal) visit. At this visit, if the family are willing, the same procedures as for the final trial visit at 6 months will be carried out. If the family is not willing, then as a minimum, the trial team will attempt to establish the reason for withdrawal.

If the child develops eczema at any point during the study, their participation in the study intervention will end as they will require treatment for the eczema. However, we will ask the family to remain in the study and attend for the final visit at 6 months where the eczema diagnosis will be re-checked to give more confidence in the chosen diagnostic criteria.

Post Intervention Questionnaire survey

Participating families are asked at their 6 month final study visit if they would be happy to be contacted in the future to see how their child is progressing. If they have agreed, the families will be sent a questionnaire survey 6 and 18 months after they have completed the intervention phase of the study, The questionnaire will establish whether the child has developed eczema and ask about any eczema treatments that have been used. Non-responders will be followed up by telephone.

SAMPLES FOR GENETIC STUDIES OF FILAGGRIN

Infants and young children are unable to spit the required 1 to 2 ml of saliva so a collection procedure developed for infants and young children will be used. A sample of saliva present in the infant's cheek pouch will be collected onto a saliva sponge either by an investigator or by the parents (both methods will be tested in this feasibility study to establish the best method for sample collection). The samples will be identified by code and shipped to the laboratory of Professor. Irwin McLean at the University of Dundee. The purpose of taking these samples in this feasibility study is to see if this aspect of the trial affects families' choices on willingness to take part in the trial. Other studies that include filaggrin gene typing have shown that it does not pose any problem to recruitment, but it needs to be included in the feasibility study to mimic what would occur in the main trial. Investigations will be limited to the five most commonly found mutations that have been linked to eczema in European populations. The methods of analysis for these five mutation variants have been published previously.[55]

DEFINITION OF INCIDENT CASE OF ECZEMA

For the purposes of this trial, we will use an adaptation of the validated U.K. Working Party Criteria[106]. The adaptations are to reflect the young age group included in the study, with regards to signs and symptoms and also chronicity. This is included in order to test the feasibility of using this definition in the main trial and can be found in appendix 1.

Procedure	Pre-trial	Screening / enrolment visit (usually pre-delivery)	Start of Trial – Baseline visit (post delivery)	Follow up telephone calls (day 10, week 6 and 18)	Follow up visit (week 12)	Final Trial Visit (week 24)	Withdrawal
Discuss trial	x	x					
Obtain informed consent		x					
Check for eligibility	x	x	X				
Randomisation			X				
Family choose emollient *			X				
Give advice on best practice skin care			X	x	x		
Give advice on emollient use *			x	x	x		
Start emollient *			x				
Discuss trial progress and any skin problems				x	x	x	x
Discuss adherence to emollient regimen**				x	x	x	x
Determine presence / absence of eczema and other skin conditions					x	x	x
Saliva sample taken for filaggrin gene typing ***					x	x	x
Semi-structured interview / questionnaire to establish parental opinion of the trial						x	x

* Intervention group only
** Adherence will be checked by weekly contact with the family
*** This will be done at EITHER the week 12 or week 24 visit or may be done earlier if family take saliva sample and post to laboratory

OUTCOME MEASURES

Primary outcome

The primary outcome measure of interest for this feasibility study will be the proportion of families willing to be randomised. This is the most critical component of the success of any future trial examining the effectiveness of this strategy for eczema prevention. The primary outcome of future investigations is likely to be the incidence of eczema at two years, but the aim of this current proposal is to gather the necessary preliminary data to successfully design a definitive effectiveness trial. We will explore whether the primary outcome is influenced by the way in which families are approached e.g. direct approach from a GP database search or through advertisements.

Secondary outcomes

The secondary outcomes are designed to further facilitate the design of a larger, controlled international multi-centre trial.

- Proportion of families eligible for the trial
- Proportion of families accepting the initial invitation to participate
- Proportion of families who found the interventions acceptable
- Reported adherence with intervention
- Proportion of families for whom the blinding of the assessor to the allocation status was not compromised
- Amount of contamination as a result of increased awareness in the control group.
- Percentage of missing data and early withdrawal rates
- Incidence of emollient-related adverse events
- Incidence of eczema at 6 months, 12 months and 24 months.
- Age at onset of eczema and the proportion which are transient cases
- Filaggrin gene mutation status

RANDOMISATION AND BLINDING

Participants will be randomised using a web-based computer generated internet randomisation service provided in collaboration with the Nottingham Clinical Trials Unit (www.ctsu.org.uk) and concealed from trial investigators. Allocations will only be released once eligible participants' details have been irrevocably entered into an online database. Randomisation will be stratified by recruiting research nurse.

The intervention (daily emollient use) is impossible to blind from trial participants so the main outcome assessor will be blinded to allocation status.

It is also likely that any mother allocated to standard care will increase their barrier protection regimen for their newborn baby after reading trial information suggesting that barrier enhancement could be effective, or by talking to parents allocated to the intervention group. At the end of the trial we will ask parents directly about change in behaviour supplemented by discussion in focus groups with a panel of trial participants. Blinding the main outcome

assessor to allocation status is possible (and essential) and its integrity will be tested in this trial by asking the assessor to guess which intervention was given to the participant.

Maintenance of randomisation codes and procedures for breaking code

Both the participating family and the co-ordinating centre are aware of the allocation to intervention or control group. The only blinding in this trial is the nurse or doctor carrying out the clinical examination to determine whether the infant has developed eczema or other skin diseases. Breaking the blind should only be done in the event of a medical emergency in which treatment for the medical emergency is dependent on knowing whether the infant has been receiving emollients. Therefore, it is unlikely for this trial that there will be a need to break the blind.

If a need should arise, the nurse or doctor will be instructed to contact the Trial Manager in the first instance who will have access to the master list, created via a web-based system hosted by the Nottingham Clinical Trials Unit. This will maintain an audit trail of any instances of un-blinded outcome assessment. The investigator will be asked to provide the date, name of person requesting the blind to be broken, a reason why and any other relevant information within 48 hours of breaking the blind.

TRIAL MANAGEMENT

A feasibility study similar to the one described here is being conducted concurrently in the US (Lead Dr Eric Simpson). Although these two studies are independent, the resulting data will be pooled in order to obtain the best available evidence on which to design the subsequent RCT.

The trial will be co-ordinated from the Centre of Evidence based Dermatology by the Trial Manager. A Trial Management Group (TMG) will meet regularly during the trial, probably every 1 to 2 months, although this will change to reflect the requirements of the trial as it progresses. The TMG will comprise the Chief Investigator and the Trial Manager with Dr Simpson and other experts and consumers invited to attend as needed.

This small trial is designed to assess the feasibility of running a subsequent RCT, rather than collect meaningful clinical outcomes and so a Data Monitoring Committee (DMC) is not deemed necessary. A Trial Steering Committee (TSC) with independent members will be convened whose role will also be to monitor safety of the study participants in the absence of a DMC. The TSC will feed back to the TMG as well as the funders as an independent body. The TSC will oversee both the US and UK studies.

DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

Families will be approached about the trial usually in the last trimester of pregnancy. If they agree to participate, then consent will be obtained during this period. Families will participate in the intervention phase of the trial for 6 months and their participation will commence within 3 weeks of birth of the infant.

Recruitment is planned to commence in February 2010 and will continue for approximately 6 months. Participants may be recruited up to 6 months prior to delivery and then followed up

for 6 months so the trial will end between February 2011 and August 2011. However, as one of the purposes of this feasibility study is to assess recruitment rates, so the recruitment period may be shorter or longer than this initial estimate.

Participants will be followed up until their 2nd birthday to check if the child has developed eczema (according to the UK working party criteria for diagnosis of eczema) since they were last seen in clinic. This follow up has been included to test:

i) the feasibility of carrying out long term follow up in the main RCT, and

ii) whether the proposed criteria for defining eczema are suitable for the main RCT.

Families will receive questionnaires at 1 and 2 years. The 2 year questionnaire may be administered by post or by telephone (depending on resources available and ability to reach the parents). To receive a diagnosis of eczema, the child must satisfy 3 out of 4 criteria, one of which is visible flexural dermatitis requiring assessment of the skin by a health professional. Therefore, where the presence of visible flexural dermatitis could determine whether or not the child meets the criteria, the family will be invited in to attend a clinic visit or a home visit for an assessment of the child's skin.

End of the Trial

The end of the trial will be defined as last participant, last visit. ~~The post intervention follow up will not be considered part of the trial.~~

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Inclusion criteria

- Participant must have a parent or sibling with a diagnosis by a doctor of any one of the following three atopic diseases:
    - Eczema
    - Allergic Rhinitis
    - Asthma
- Infant in overall good health
- Mother must be at least 16 years of age at delivery
- Capable of giving informed consent

Exclusion criteria

- Mother taken any pro-biotic supplements containing Lactobacillus rhamosus during pregnancy, or plans to take any whilst breastfeeding
- Preterm birth defined as birth prior to 37 weeks gestation
- Major congenital anomaly
- Hydrops fetalis

- Any immunodeficiency disorder
- Any severe genetic skin disorder
- Any other serious condition that would make the use of emollients inadvisable.
- Any other major medical problems that the investigator deems may increase the risk of adverse events with the intervention or in whom assessing the outcomes may be masked by the underlying problem or practically very difficult to assess.

In the case of a multiple birth, the first born child will be chosen as the index child.

TRIAL TREATMENT AND REGIMEN

General skin care education and soap substitute

Cleansers and bathing habits can alter skin barrier function, although the effects of emollient therapy are likely to greatly outweigh the effects of cleansing. All families will receive instructions on the bathing and cleansing of their infant and these will be standardised to minimise investigator counselling and inter-investigator variability. The instructions will be in accordance with standard guidelines and will include the following:

- Bathing may occur up to daily (determined by the family), but soap, bubble bath and bath additives should be avoided. Families will be advised to purchase and use a soap substitute and will be provided with vouchers to facilitate this. They will be asked to use this instead of any soap when bathing and washing the infant.
- Only a mild, frequent wash shampoo should be used and families should avoid covering the infant's body in suds when rinsing.
- Avoid the use of lotions and baby wipes especially on face and hands. Families will be encouraged to avoid using lotions and baby wipes for nappy changing.
- When feeding solids to the infant, families will be encouraged to apply emollient first to protect, then to use a wet flannel to wipe face and hands clean then re-apply emollient afterwards.

Allergy avoidance advice

All families will be given information with regards to reducing the incidence of eczema and allergies in accordance with current NHS guidelines and will include the following:

- Mothers will be encouraged to breastfeed, if possible, up to at least 6 months of age.
- For infants younger than 6 months who are not breastfed, parents will be informed that there are some data showing that hydrolyzed formulas may slightly reduce the chance of developing eczema. The choice of infant formula will be left to the discretion of the family and the GP.
- Parents will be encouraged to avoid solid foods until after the age of 6 months.

Emollient use

Emollients, either creams or ointments, improve barrier function by supplying the stratum corneum with water and lipids; however, the exact mechanisms in which emollients exert their effects are unknown.[73-75] Ointments contain lipids and lipid-like structures such as

hydrocarbons, free fatty acids, long-chain alcohols, cholesterol esters, and triglycerides. Creams are mixtures of oil and water and provide hydration to dry atopic skin in addition to lipids.

Emollient effects vary according to oil and water proportions, lipid composition, and the presence or absence of certain moisturizing factors, such as urea. Moisturizing factors enhance the water-binding properties of the stratum corneum.[42,98] Creams exert a hydrating effect by liberating water from the formulation itself.[99] The occlusive effect of oil-based formulations can trap water in the stratum corneum, thus increasing hydration. No one emollient formulation has proven superior in improving barrier function. [42,98]

The emollient is to be used on their infant's entire skin surface at least once a day especially after bathing, beginning within 3 weeks of the birth of the infant. It is unlikely that parents will wish to apply the emollient to the scalp as this will make hair greasy, so application to the scalp will be optional. In addition, parents may not wish to use around the nappy area as the application of emollients can affect the absorption of nappies. Parents will be encouraged to apply to the nappy area, but again, this will be optional.

Parents may require different emollient textures and viscosity dependent on body site, age, climate and cultural preference. We have initially included three emollients that vary in texture and viscosity. However, as this is a feasibility study, if none of the three emollients are acceptable to the families, then we will offer other emollients that are widely available. In a prevention study of this type, parental acceptance and adherence to treatment regimen are of paramount importance and this flexible approach will allow a confident decision to be made regarding the choice of emollients for the subsequent main RCT.

The preferred three emollients for this study are:

Least greasy 	**Sunflower seed oil**	Has the 'natural' aspect that many parents like. Has shown to repair the skin barrier in damaged mouse skin, better than other oils including mustard, olive and soybean oils.[102] Three randomized controlled trials showed a reduction in neonatal mortality and nosocomial infections in preterm infants with the use of sunflower seed oil on the skin for 2 weeks.[86,87,103]
	Doublebase	Oil in water emollient which is widely used in the UK for the treatment of eczema. Two studies have shown Cetaphil Cream (a similar preparation) improves skin barrier function, even when used on the face in sensitive skin patients.[100,101]
	white soft paraffin/liqued paraffin 50:50	Low cost so may have particular relevance for worldwide use. One small case-control eczema prevention study used petrolatum. In the first study of emollient use in premature neonates, Aquaphor (similar preparation) improved skin barrier

Most greasy		measurements, decreased the incidence of "dermatitis," and reduced bacterial colonization in premature neonates, who are known to have defective skin barriers.[85]

Whilst mono-therapy will be encouraged, participants will be able to change during the trial or use more than one at a time for different areas of the body or different times of the day. Reasons for choice of emollient will be recorded.

Concomitant medications

Families in the study will be advised to not use emollients other than those provided for the trial.

The use of other treatments for skin problems will be discouraged. Parents will be advised to call the trial team if they have concerns about their infant's skin and use moisturisers in the first instance. The family will be invited to attend for a visit if there is a persistent rash or itch to determine if the infant has developed eczema. It is unlikely that parents would commence undirected over-the-counter topical hydrocortisone treatment on a young baby, but if this does occur, then the use will be recorded.

If a prescription-strength topical steroid or other anti-inflammatory therapy is needed for any eczematous eruption on the body, that participant will be labelled as meeting criteria for eczema unless a clear diagnosis other than eczema can be made, such as contact dermatitis. Use of any treatment will be recorded. The control group will be encouraged to not use emollients unless dry skin develops, in line with current guidelines and it's use will be recorded.

Adherence

Participating families in the intervention group will be asked to complete a daily adherence chart with details of frequency of application. In addition, families in the intervention group will receive a frequent text message or email asking about adherence to treatment. Adherence will be discussed with the family at the follow up visits.

STATISTICS AND SAMPLE SIZE

The purpose of this feasibility study is not to estimate treatment effect, but to estimate the proportion of eligible families, the proportion willing to be randomized and acceptability of the intervention. It is estimated that around 40% of all families screened will have a history of atopic disease that predispose to a high risk of eczema in their offspring. Around 250 families will need to be screened for eligibility in order to identify around 100 families (40%) at high risk of giving birth to a child with atopic disease. One hundred families will provide a sufficiently precise (within 10 percentage points for a 95% confidence interval) estimate of the proportion willing to be randomized, assuming between 40 and 60% are willing to be randomised. The remaining outcome measures will then be assessed in those that are randomised.

The analysis, carried out by the study team at the University of Nottingham, will be largely descriptive in nature and thus require no further analysis. The intervention group will be treated as one pooled group regardless of which of the three emollients they used.

Success criteria that will indicate whether the feasibility study should proceed to larger controlled trial are the following:

- A lower 95% confidence interval of at least 30% of eligible families willing to be randomised
- A lower 95% confidence interval of at least 70% of randomised families who found the interventions acceptable
- A lower 95% confidence interval of 80% for the proportion of outcome assessments that have remained blinded
- Less than 30% missing data and drop-out rates

The results of the trial will be compared to these criteria for success and a decision will be made regarding proceeding with a larger definitive RCT.

ADVERSE EVENTS

Definitions

An adverse event (AE) is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

An AE does include a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after trial drug administration even though it may have been present prior to the start of the trial.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
2. pre-existing disease or conditions present or detected at the start of the trial that did not worsen.
3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. overdose of concurrent medication without any signs or symptoms.

A **Serious Adverse Event (SAE)** is any adverse event occurring that results in any of the following outcomes:

- Death
- life-threatening
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability / incapacity
- A congenital anomaly or birth defect in the offspring of a participant
- Other medical events may be considered to be a SAE if they require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality (not related, possibly related, probably related or definitely related). An adverse event whose causal relationship to the trial drug is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Reaction (AR). If the AR is classed as serious then it is a Serious Adverse Reaction (SAR). A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the trial medication or treatment is not the cause.

Causality

Not related or unlikely: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation. This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the trial intervention is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of Adverse Events

For this feasibility study, only a limited number of adverse events that could possibly be related to the use of emollients will be collected. The purpose of collecting these is to test the feasibility of recording and collecting this information for the main RCT.

The following adverse events will be recorded:

- Folliculitis
- Skin infections
- Hypersensitivity reactions
- Accidents that involved any form of slippage

All treatment related serious adverse events will be recorded and reported to the REC as part of the annual reports. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

Trial Treatment / Intervention Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment or intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment or intervention shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant Removal from the Trial due to Adverse Events

Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the Investigator.

ETHICAL ASPECTS

ETHICS COMMITTEE 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) department. 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 and GP 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 participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced.

During the third trimester of pregnancy, the investigator or nominee will discuss the trial with the family and also give them a copy of the Participant Information Leaflet which will contain all the details of the trial. There will be opportunity for the family to ask questions about the trial and the investigator or nominee will ensure the questions are fully answered.

The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before participating in the trial. The original will be kept in the Investigator Site File, one copy given to the participating family and a copy will be retained in the participant's hospital or GP records.

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

The investigator will inform the participant 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).

As this trial includes minors, the conditions and principles listed in Part 4 of Schedule 1 to the Clinical Trial Regulations pertaining to informed consent will be adhered to. This will ensure that:

- The family is fully aware of all aspects pertaining to their inclusion in the trial including the objectives, risks and inconveniences of the trial from the discussion and the participant information given.
- Contact details will be provided for further information in the participant information.
- The right to withdraw the child from the trial, without the child being subject to any resulting detriment will be highlighted to the family.

RECORDS

Case Report Forms

Each participating family will be assigned a trial identity code number, allocated at screening, for use on the case report forms (CRFs), other trial documents and the trial database. The database will also use the initials of the infant (of first and last names separated by a hyphen or a middle name initial when available) and date of birth.

CRFs will be treated as confidential documents and held securely in accordance with regulations. A separate confidential record will be kept of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Participant Screening and Enrolment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Site Responsibility (Delegation) Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated. The person completing the forms shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

The CRFs will be the source data for this feasibility study. A check of the hospital notes for the infant will occur to check the eligibility criteria are met with regards to the health of the infant. A letter will be sent to the infant's GP and a note will be placed in the infant's hospital records describing the study and explaining their participation. The GP will be notified of any significant adverse reactions.

Direct access to source data / documents

The case report forms will made be available at all times for review by the Chief Investigator, Sponsor's designee and audit inspection.

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 information required for the purposes of the trial. CRFs will be held securely, in a locked cabinet. Access to the information will be limited to the trial staff and investigators and audits. Computer held data including the trial database will be held securely and password protected. Access will be restricted by user identifiers and passwords.

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.

There will be regular contact between the participating families and the co-ordinating centre which requires a database to be kept of contact details. Families will give their explicit consent for this to happen and all medical details will be kept separately from this database.

Electronic data will be backed up every 24 hours.

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.

Nottingham University Hospitals NHS Trust contributes to the NHS Clinical Negligence Scheme for Trusts (CNST) which provides indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

This trial will be conducted in adherence with the protocol and International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP).

Training days will be arranged for recruiting centres and the UK CRN research nurses working on the study. It will cover all relevant aspects of GCP and all study procedures and SOPs.

An audit of the Trial Master File for inclusion of essential documents as defined by GCP will be conducted by the Trial Manager or designee at least yearly and an audit report shall be made available to the Trial Management Group.

Auditing of the trial will be at the discretion of the individual Trust Research Governance Departments under existing governance arrangements.

TRIAL DATA

Central monitoring of the data will be carried out by the Trial Manager before entering into the trial database. This study has been classed by the MHRA as not a Clinical Trial of an

Investigational Medicinal Product and is very low risk and so no on-site monitoring is planned by the sponsor.

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

RECORD RETENTION AND ARCHIVING

In compliance with the GCP guidelines, regulations and in accordance with Nottingham University Hospitals Trust policy, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 10 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File, trial documents and database will be held by the Chief Investigator on behalf of the Sponsor. They shall be finally archived at secure archive facilities at the University of Nottingham.

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 management Group and Trial Steering Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol. 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

The study results will be published in a peer reviewed journal and will be used to design the main RCT. Participants will not be identified in any publications.

USER AND PUBLIC INVOLVEMENT

Members of eczema support groups and a panel of parents of children with eczema have reviewed and commented on the study design and their comments taken into consideration. One of the purposes of this trial is to get input from the participating families into the design of the main RCT.

TRIAL FINANCES

Funding source

This trial is funded as part of a programme grant from the National Institute of Health Research.

Participant stipends and payments

Participants will not be paid for taking part in this trial. Any out of pocket travel expenses, will be reimbursed. Families wishing to take part in the post study questionnaire survey will be offered an inconvenience allowance in the form of a £10 Boots voucher.

APPENDIX 1

The following definition is an adapted version of the previously validated U.K. Working Party Criteria, instrument.[105] This will be used to establish an **incident case of eczema** during the study:

Eczema	A history of an itchy skin condition for at least 2 days a week for the past 4 weeks plus three or more of 1. a history of a rash in the skin creases (folds of elbows, behind the knees, fronts of ankles or around the neck), forearms or lower legs. Symptoms must have been present for at least one month either continuously or intermittently unless a topical anti-inflammatory therapy for symptom relief was required. If so, symptoms may have been present for a shorter duration. 2. a personal history of asthma or hay fever or a history of atopic disease in a first-degree relative 3. a history of a generally dry skin since birth 4. visible flexural dermatitis as defined by a photographic protocol and/or visible dermatitis on the forearms or lower legs with absence of axillary involvement. Visual confirmation of eczema diagnosis by a clinician, dermatology nurse or a research nurse suitably trained in recognising the symptoms of eczema is preferred. Any infant fulfilling these criteria but who, on examination by a suitably trained health professional are deemed to have a different skin disease will be classified as not having eczema.

SIGNATURE PAGE

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

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