A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE)

University of Utah IRB Protocol Number: 00106351
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Principal Investigator: Eric Simpson
NIAMS Program Official: Ricardo Cibotti
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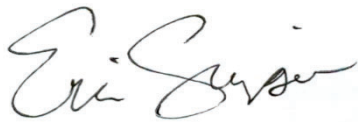
STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIAMS Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 6/4/2021

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Title: Associate Professor

Version Number	Version Date	Summary of Revisions Made:
1.0	24Feb2016	Original version
2.0	24Feb2017	Resubmission version
3.0	01Dec2017	Consent revision
4.0	16Jan2018	Consent revision
5.0	16Apr2018	Revisions in response to Data Safety Monitoring Board
6.0	25May2018	Budget adjustments and Data Safety Monitoring Board revision request
7.0	25Jul2018	Adjust shipping timeline in response to deviation
8.0	21Dec2018	Continuing review and new recruitment strategies
9.0	18Feb2019	Duke recruitment strategies and Data and Safety Monitoring Board revision recommendations
10.0	03May2019	Revised inclusion criteria to allow participation via e-mail or text message
11.0	05Aug2019	Select CeraVe cream at baseline for participants who do not select the preferred moisturizer
12.0	14Nov2020	Patient portal messages for site recruitment
13.0	04Jun2021	Analysis plan adjusted with removal of interim analysis

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LIST OF ABBREVIATIONS

AAD	American Academy of Dermatology
AD	Atopic Dermatitis
AE	Adverse Event/Adverse Experience
BEEP	Barrier Enhancement for Eczema Prevention
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federalwide Assurance
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOOP	Manual of Operating Procedures
N	Number (typically refers to participants)
NIAMS	National Institute of Arthritis, Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PBRN	Practice-based Research Network
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
TEWL	Transepidermal Water Loss
UP	Unanticipated Problem

PROTOCOL SYNOPSIS

Title	A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE) Eric Simpson, MD, MCR, Principal Investigator
Study Design Intervention to be tested, brief description of protocol	This is a pragmatic, multi-site, randomized community-based trial in which dyads of a parent or legal guardian ("parent") and an infant age 0 to 2 months are enrolled. Participating dyads are randomly assigned to receive lipid-rich emollient with instructions for daily use to infants plus routine skin care instructions (intervention group) or routine skin care instructions alone (control group). Both groups will receive mail, e-mail and text message reminders to follow protocol instructions based on their group allocation until the infant reaches 24 months old. Dyads complete brief surveys quarterly with more complete survey instruments at 12 months and 24 months. Primary care clinicians trained in using standard atopic dermatitis (AD) diagnostic criteria will document presence of AD at all visits, including scheduled well child visits or at any other unscheduled visits, which will be abstracted from the health record.
Intervention dosage and frequency	Previous studies found petrolatum-based emollients applied to the skin improve barrier function (transepidermal water loss [TEWL] and hydration), decrease the effects of skin irritants, and improve clinical outcomes. Five emollients shown to improve barrier function or have simple formulations with petrolatum are used in the study: CeraVe Healing Ointment Petrolatum (e.g., Vaseline) Cetaphil cream CeraVe cream Vanicream Parents assigned to the intervention arm will receive a lipid-rich emollient and educational materials promoting once daily full-body emollient use until their infant is 24 months old. Parents will select an emollient to be mailed to the dyad's home at enrollment and approximately every six months for the duration of the study; parents may change emollients during the course of the study. Parents assigned to the control arm will receive educational materials promoting general infant skin care guidelines only and will be asked to refrain from emollient use unless dry skin develops (current standard of care guidelines). Parents will receive text messages and e-mails directing them to educational materials and materials will be mailed to the parent's home. Both study arms will have access to educational materials, and will receive text messages or e-mails two weeks after enrollment and during quarterly and annual surveys reinforcing infant skin care messages related to the study arm to which they are assigned.

Primary and Secondary Endpoints	Primary Outcome:
	The cumulative incidence of AD at 24 months of age as recorded in health records. Clinicians will be trained to use the American Academy of Dermatology (AAD) Consensus Criteria for diagnosing pediatric AD. Clinicians will assess for AD at each clinic visit and record in the health record.
	
	Secondary Outcomes:
	• Parental report of provider-diagnosed AD
	• AD as diagnosed by the Children's Eczema Questionnaire (CEQ)
	• Parental report of sleep loss of the infant reported as average number of days per week (1 week recall) of disrupted sleep in their infant measured at 12 and 24 months
	• Any prescription topical medication use of over-the-counter hydrocortisone usage recorded by parent or recorded from records review by research coordinator at 24 months
	• Asthma risk using a modification of the Asthma Predictive Index and International Study of Asthma and Allergies in Children questionnaire
	• Parental report of immediate food allergy symptoms
	• Parental report of a provider diagnosis of food allergy that was confirmed by prick testing or IgE blood test.
	• Global Health Status using one question from the PROMIS Pediatric Global Health (PGH-7) instrument
	• In infants who develop AD:
	  ○ Time to onset of AD as measured by parental report of eczema age of onset
	  ○ Time to onset of AD as measured by provider-recorded date of first diagnosis retrieved from record review of health record
	  ○ AD symptom severity (e.g. itch) as reported by the patient-oriented eczema measure (POEM) instrument
	  ○ Parent-reported global severity of eczema assessment
	  ○ Infant Dermatology Quality of Life Instrument (IDQOL)

Study Population	From our planning period and recent population-based 2-year prevalence in the U.K., we expect the cumulative incidence of AD in the control to be ~24% at two years of age. To estimate at least 30% relative reduction in AD, we require 1,044 dyads (522 per group) to achieve 80% power for a two-tailed test at the 0.05 level of significance. Allowing for an approximately 20% loss to follow-up, we plan to enroll 1,250 babies (625 per arm). 1,250 parent/infant dyads will be enrolled from 35 community-based family medicine and pediatric practices from practice-based research networks (PBRNs) in Colorado, Oregon, North Carolina, and Wisconsin. These PBRNs are part of the Meta-network Research And Learning Center (Meta-LARC). Each clinic will be asked to enroll two or more dyads per month for approximately two years, for a total of 50 dyads per clinic. Enrolled dyads will be representative of the gender, race and ethnicity of patients receiving care in participating clinics. Clinical Site Hubs (practice-based research network, PBRN)

	• Oregon Rural Practice-based Research Network – *Oregon Health & Science University* • State Networks of Colorado Ambulatory Practices & Partners – *University of Colorado* • Wisconsin Research & Education Network – *University of Wisconsin* • Duke Primary Care Research Consortium – *Duke University*
Inclusion / Exclusion Criteria	All dyads who meet inclusion/exclusion criteria will be eligible for study participation. <u>Inclusion Criteria</u> In order to be eligible to participate in this study all of the following criteria must be true for the dyad: 1. Parent can provide electronic signed and dated informed consent form. 2. Parent is willing and able to comply with all study procedures for the duration of the study. 3. Parent is a primary caretaker of an infant 0 to 2 months of age. 4. Parent is 18 years of age or older at time of consent. 5. Parent can speak, read, and write in English or Spanish. 6. Parent has a valid e-mail address or phone that can receive text messages 7. Parent has reliable access to the internet. 8. Infant is a patient of a participating Meta-LARC clinic site at the time of consent. <u>Exclusion Criteria</u> A dyad who meets any of the following criteria will be excluded from participation in this study: 1. Infant was born at less than 25 weeks gestational age. 2. Infant has established eczema as diagnosed by the primary healthcare provider at clinic site of enrollment per parent report. 3. Infant has known adverse reaction to petrolatum-based emollients. 4. Infant has an immunodeficiency genetic syndrome such as Wiskott-Aldrich Syndrome or Severe Combined Immunodeficiency Syndrome. 5. Infant has extremely low birth weight (less than 1000g or 2.2 lbs [2 pounds 3 ounces] at birth). 6. Infant has a sibling enrolled in the study. 7. Parent is unwilling or unable to comply with study procedures.
Recruitment Plans	<u>Sampling Plan:</u> It is anticipated that 2,500 dyads will need to be screened in order to reach the target enrollment of 1,250 dyads. The number for target enrollment accounts for attrition. <u>Recruitment Plan:</u> Dyads will be recruited from 35 PBRN member clinics in four states. Staff at PBRN clinics will approach parents with an infant age 0 to 2 months presenting to a scheduled clinic visit in person, via mail, phone (Duke University only) or via patient portal. Parents will review study information on a clinic-based tablet computer. Rack cards or postcards with link to the enrollment website will be provided for those that do not enroll via tablet. Study materials will be available in English and Spanish. Any

	questions about the study will be directed to a toll-free number operated by the clinical coordinating center (CCC). Parents will respond to inclusion/exclusion criteria questions. Screening: Dyads will review an electronic information sheet and agree to be screened. Dyads will be directed to respond to screening questions. Eligible dyads will provide contact information. Informed Consent Process: Eligible parents will be directed to the electronic consent form. After reading the consent form, participants who have no questions will continue on to sign the consent form. Participants who do have questions about the project will be directed to call research staff via a toll-free number to discuss the project and review questions; if a participant does not call research staff, research staff will initiate a call to the participant to complete consent procedures. Once participants' questions are answered, participants will continue to sign the consent form. Consented will be provided via electronic signature online, either at the clinic via computer tablet or at home via internet-enabled phone or home computer. The electronic consenting process follows all IRB requirements for electronic consent. Informed consent will be obtained by one parent or legal guardian. Consented parents will receive a copy of their signed consent form by e-mail. Child assent will not be obtained, as infants are unable to provide assent. Enrollment Plan: Consented dyads will be directed to complete screening and enrollment questionnaire. Those unable to complete the survey at that time will be sent a link via e-mail and may receive phone or text message reminders to complete questionnaires via internet-enabled phone or home computer. Research coordinators from each of the four PBRNs will meet weekly to monthly (face-to-face or by phone) with each clinic to resolve recruitment challenges with clinic staff, to observe clinical workflows, to identify recruitment opportunities.
Study Organizational Structure	The study is organized into two main bodies with oversight from the PI. Those bodies include the clinical coordinating center (CCC), the data coordinating center (DCC). The CCC administers the daily activities of the project, including protocol maintenance, selection criteria, clinician training, participant communication, data collection, statistical analyses, and study oversight. The DCC maintains the study database and conducts data management, is responsible for enrollment and randomization, intervention delivery, maintains data quality assurance, initiates participant reminders, and initiates surveys with participants. The DCC and CCC oversee and work in partnership with PBRN leadership to promote recruitment and retention, ensure training of participating clinicians, update participant contact information, complete data quality activities and collect primary outcome data from the infant's health record through 27 months.

	The study protocol was developed utilizing input from multiple stakeholders organized into a Community Advisory Committee and a Scientific Advisory Committee. These committees will guide various aspects of study implementation as needs arise.
Retention Plans	Each PBRN research coordinator will meet regularly with clinic staff to keep clinic staff engaged in the study and monitor routine documentation of AD. The DCC will track survey completion and utilize effective evidence-based methods to maximize cohort retention. Methods to use include financial incentives, pre-notification of surveys, and web surveys containing images. Outreach to participants will include telephone support from the CCC. Participants will be eligible to receive $135 for completing three surveys during approximately 24 months of study participation. The compensation schedule will incentivize the completion of questionnaires to enhance participant retention. Dyads randomized to the intervention group will also receive 24 months' worth of emollient. The enrollment questionnaire gathers contact information of alternate contacts who may help locate the participant if they become unresponsive during the study. During quarterly and annual contacts, participants will be asked to confirm or update their current contact information. If participants become unresponsive, research coordinators may also update contact information from clinic records.
Group Assignment	Dyads will be automatically randomized after the parent has completed enrollment. Randomization will be performed by the central DCC using a computer-generated randomization schedule. Randomization will be stratified by clinic and parent-reported history of atopic disease in the infant's first-degree relatives at the time of randomization to ensure balance within sites and groups. Randomized participants will then be directed to web-based instructions available for downloading. Materials will be mailed to the participant's home along with study payment. Participants who withdraw or are terminated from the study will not be replaced with a new participant. The proposed dyad recruitment numbers account for attrition. Withdrawal and termination outcomes will be recorded in the study database.
Subject Participant Duration	Dyads participate in the project until the infant is 24 months of age, or for about two years. Visits are outlined in the schedule of events.

Schedule of events Procedures		Screening (≤ 2 Months)	Contact 1 (< 2 Months)	Contact 2 (3 Months)	Contact 3 (6 Months)	Contact 4 (9 Months)	Contact 5 (12 Months)	Contact 6 (15 Months)	Contact 7 (18 Months)	Contact 8 (21 Months)	Contact 9 (24 Months)
Consent		•	•								
Assessment of Eligibility (Inclusion/Exclusion criteria)		•									
Baseline	Demographics		•								
	AD Risk		•								

	Living Environment		•								
	Pet Ownership		•								
	Alternate Contact		•								
Provide/Update Contact Info			•	•	•	•	•	•	•	•	
Quarterly Contact	Confirm PCP			•	•	•	•	•	•	•	•
	AD diagnosis			•	•	•	•	•	•	•	•
	Study arm adherence			•	•	•	•	•	•	•	•
Choose and ship emollient (Intervention Group Only)			(•)		(•)		(•)		(•)		
Assessment of AE/SAE				•	•	•	•	•	•	•	•
Annual Questionnaire	mAPI and ISAAC						•				•
	CEQ						•				•
	Sleep loss						•				•
	Allergies						•				•
	Study arm adherence						•				•
	Medication history						•				•
	PGH-7 Global Health						•				•
	Infant diet						•				•
	Emollient acceptability (Intervention Group Only)						(•)				(•)
	If infant develops AD: -AD age of onset -Global severity of AD -IDQOL -POEM						(•)				(•)
Chart Abstraction	AD or eczema diagnosis by HCP						•				•
	Intensity of AD						(•)				(•)
	Medication history						(•)				(•)
	Other allergy diagnoses						(•)				(•)
	Assessment of AE/SAE						•				•

Visit Schedule: Participating dyads will not have in-person visits with the study team. Annual questionnaires will be administered by e-mail or text message at enrollment and when the infant is 12 and 24 months old. Every three months, participants will receive a quarterly survey sent via e-mail or text message and a reminder of the randomization arm. A reminder of randomization arm will be sent two weeks after enrollment. Text and phone reminders will occur at baseline and for annual surveys.

Data Collection: A brief anonymous screening survey will be given to potential participants. Eligible participants will be then be prompted to provide contact information that will be linked to the screening survey. All surveys will be collected through internet-based online survey with reminders sent via e-mail or text message. Toll-free phone numbers will be available to dyads to assist with data collection.

Health record abstraction: PBRN research coordinators who are blinded to study arm assignment will abstract data from participating infants' health

<table>
<tr><td></td><td>records through 27 months to review for adverse events, diagnosis of AD, treatment of AD, and clinician diagnosis of allergies. The cumulative incidence of AD at 24 months of age will be compared between the intervention and control arms.

<u>Outcome Assessments:</u> AD assessment performed by a trained clinician at well child through 24 months of age. Other outcomes will be assessed via parental electronic questionnaires at 12 and 24 months.</td></tr>
<tr><td>Study Duration</td><td>Total study duration will last for five years, with enrollment projected to be completed during the second year of the study. An interim analysis will occur in quarter 1 of year 4 when 50% of participants have completed 2-year follow-up. All participants will complete year 2 follow-up by the end of study year 4. Final data analyses will occur during quarters 1-3 of year 5 with final reporting, manuscript development and study clinic site reports to follow.</td></tr>
<tr><td>Availability of Investigational Product and IND/IDE Status</td><td>The Food and Drug Administration has determined investigational new drug (IND) exemption and investigational drug exemption (IDE) as appropriate for the proposed trial (See Protocol Appendix G for IND exemption). Emollients used in the trial registered as over-the-counter drugs (i.e. with an active ingredient listed) qualify for an IND exemption, which is CeraVe Healing Ointment and petrolatum.

Emollients registered as cosmetics will require an IDE. Emollients used for the study include Cetaphil cream, CeraVe cream and Vanicream.

The manufacturing companies for the higher cost emollients will supply 1,000 jars containing 400-454g of emollient over the 4-year course of the study.

<table>
<tr><th>Emollient</th><th>IND</th><th>IDE</th><th>Manufacturer</th><th>LOS</th></tr>
<tr><td>CeraVe Healing Ointment</td><td>XX</td><td></td><td>L’Oreal</td><td>Yes</td></tr>
<tr><td>Petrolatum (e.g., Vaseline)</td><td>XX</td><td></td><td>Unilever</td><td>No</td></tr>
<tr><td>Cetaphil cream</td><td></td><td>XX</td><td>Galderma</td><td>Yes</td></tr>
<tr><td>CeraVe cream</td><td></td><td>XX</td><td>L’Oreal</td><td>Yes</td></tr>
<tr><td>Vanicream</td><td></td><td>XX</td><td>Vanicream</td><td>Yes</td></tr>
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KEY ROLES AND CONTACT INFORMATION

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1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

The prevalence, socioeconomic costs, comorbidities and impact on children and families make the prevention of atopic dermatitis (AD) an important public health goal. Our previous work found AD affects approximately 13% of children under the age of 18 years old in the United States[1]- a similar prevalence to many areas of the world.[2] In all continents, the prevalence of AD continues to rise for unknown reasons, but suggests environmental factors are partly responsible.[3] The vast majority of cases begin within the first two years of life, although onset may occur at any age. Many children with mild disease outgrow their disease; however, the number of children who experience persistence into adulthood is likely underappreciated.[4]

Children with AD suffer from chronically inflamed skin lesions accompanied by unrelenting pruritus. Skin lesions often have oozing and crusting predisposing the skin to secondary bacterial infection. Studies reveal the impact of AD on a child's quality of life is profound. Children with AD have more disturbed sleep, difficulty in school, and more behavioral problems compared to healthy controls.[5] The family impact of the disease is similar to having a child with diabetes.[6] Our group and others have found an increased risk of neurodevelopmental disorders such as attention-deficit-hyperactivity disorder in children with AD as well.[1,7] Annual health care expenditures for AD are also significant, estimated at $3-5 billion annually in the U.S., similar to those of other chronic childhood diseases such as asthma.[8] An effective AD prevention strategy would alleviate a very common health problem impacting children and families to an alarming degree. In addition, a low-cost strategy represents a good return on investment as it could provide substantial savings to the healthcare system.

1.2 Rationale for a Barrier Approach to Prevention

A greater understanding of the pathogenesis of AD creates an opportunity for a novel approach to prevention. It is now appreciated that skin barrier dysfunction plays a central role in disease pathogenesis. The etiology of this barrier function may vary between individuals. In some cases, defects in skin barrier genes may be the primary driver of skin barrier dysfunction. The seminal work by Irwin McLean's group in Dundee found loss-of-function mutation defects in filaggrin (FLG gene) to be the strongest predictor of AD ever found.[9] Filaggrin deficiency leads to increased transepidermal water loss (TEWL) prior to eczema development, reduced cutaneous hydration, and an increase in transcutaneous penetration of environmental irritants and allergens thus initiating skin inflammation.[10,11] While a groundbreaking discovery, FLG mutations do not explain the majority of AD cases in a given population.[12] Thus, skin barrier dysfunction in many cases of AD may be initiated either by other genetic defects in the skin barrier (e.g. corneodesmosin or claudin-1[13,14]) or by sub-clinical skin inflammation in children with a predisposition to exaggerated immune responses.[15] Some authors suggest modern skin care practices dry out the skin and alone can initiate skin inflammation.[16,17] Importantly, Irvine and colleagues recently found skin barrier dysfunction in the first 2 months of life to be the strongest predictor of AD development

at 2 years independent of filaggrin genotype or family history. [18] These findings were confirmed by Ohya and colleagues in a separate cohort of 118 infants in Japan.[19] Once early skin inflammation is initiated, a cycle of skin barrier dysfunction and inflammation ensues. Inflammatory infiltrates and Th2 cytokines then alter the expression of several important components of the skin barrier.[20,21] This may explain why skin barrier dysfunction can be found in patients with AD regardless of filaggrin status.[22] Barrier enhancement early in life could not only correct skin barrier defects that are the direct results of a mutation in skin barrier genes, but should also correct skin barrier dysfunction resulting from harsh bathing practices or other environmental insults. In addition, emollients have anti-inflammatory effects that could suppress early sub-clinical inflammatory infiltrates that may also initiate the disease.[23] This idea is supported by the fact that emollients prevent flares of AD in populations not selected for filaggrin status and our pilot data shows a protective effect of emollients independent of FLG status.[24,25]

1.3 Previous Trials Using Emollients for AD Prevention

The positive data from previous small trials using emollient-based therapy from birth support the need for larger trials of a barrier approach to prevention. Daily emollient therapy has been utilized and published in three prior clinical trials consisting of 264 newborns at high-risk for the development of AD and showed a significant protective effect with no adverse effects.[26-28] In the first study of its kind, we performed a pilot trial of daily emollient therapy (Cetaphil cream) involving 22 neonates at high risk for the development of AD. High risk was defined as a first-degree relative with an atopic disease and a parent with a history of AD. At least 30% of this high-risk population would be expected to develop AD in the first 1 year of life according to previous prevention trials with similar inclusion criteria.[29-31] Some studies found an AD incidence in this population to be as high as 46-62% at one year.[32,33]

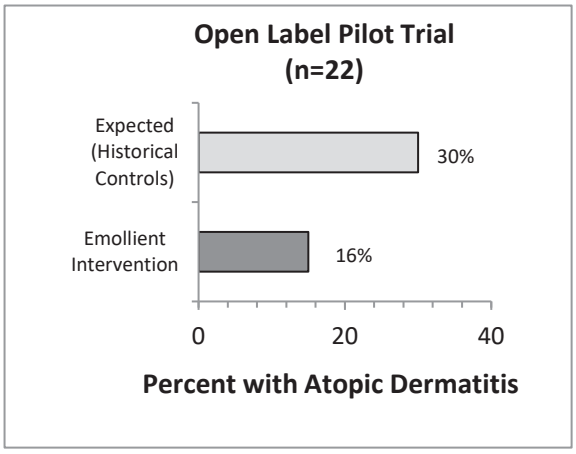

Figure 1. We performed an open-label pilot trial of Cetaphil cream in high-risk neonates. This approach was found to be safe and feasible and there appeared to be a reduced incidence of AD compared to historical controls.

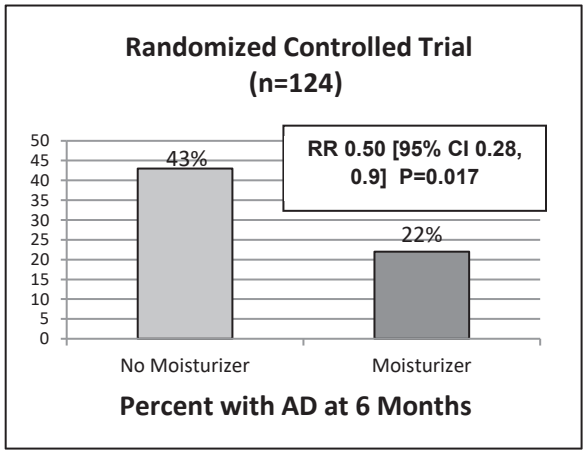

Figure 2. Results of our randomized controlled trial (n=124) of daily emollient therapy from birth. A significant reduction in AD cumulative incidence at 6 months was found in the emollient arm compared to the control arm.

This initial uncontrolled study found that only 3 of 19 (16%) infants developed AD after a

median follow-up time of over 1 year, with 3 babies lost to follow-up (Fig. 1).[26] Reported adherence was excellent (85%) and no significant adverse events occurred. These preliminary results prompted the development of an international randomized controlled feasibility trial involving our group at Oregon Health & Science University (OHSU) and four sites in the U.K.[27] One hundred twenty-four high-risk neonates were randomly allocated to one of three emollient choices in each country or to no emollient. In the U.S., emollient choices included Aquaphor, Cetaphil cream, or sunflower oil. In the U.K. emollient choices were Doublebase, Diprobase, or sunflower oil. At 6 months, 85.2% of participants reported using the intervention at least 5 times per week. The emollient intervention group experienced a 2-fold reduction in the 6-month cumulative incidence of AD (Fig. 2). Thirteen percent were lost to follow-up. These results remained unchanged when filaggrin gene status was taken into account with regression analyses. As a sensitivity analysis, a multiple imputation approach was used to account for missing data which confirmed the primary analysis (OR 0.33 [95% CI 0.23-0.42, P<0.0001]. Horimukai, et al. performed the only other published clinical trial evaluating emollients for AD prevention.[28] This study from Japan confirmed the findings of our BEEP trial finding emollient use in high-risk infants significantly reduced AD development by 32% at week 32. Similar to the BEEP trial, this was a small study (n=118) performed in a high-risk population. While results of these trials are encouraging, trials in larger and *unselected* populations are needed to determine whether this approach can be beneficial to larger populations.

1.4 Development of Protocol

Consistent with practice-based research principles, the study protocol was developed utilizing input from multiple stakeholders organized into a Community Advisory Committee and a Scientific Advisory Committee as well as key feedback from practice-based research network (PBRN) directors. During the development of the study protocol, study procedures including enrollment and measuring of outcomes were piloted in a “model recruitment” study designed to mimic the procedures for the main trial and informed the procedures and outcomes described in this protocol.

1.5 Potential Risks and Benefits

1.5.1 Potential Risks

The emollients used in our current proposed study will be used in a similar fashion to how they are being used currently by the general public with only slight changes that should not change the safety profile of the emollients. Data from two published studies and our unpublished data reveal over 70% of parents are already using moisturizers on a daily basis on their infants.[34,35] These data reveal parents primarily use watery lotions. Our hypothesis is that a basic moisturizer with higher lipid content than a typical lotion will reduce the risk of developing atopic dermatitis by providing better barrier repair than water-based lotions. We also hypothesize that more frequent use of a thicker emollient (i.e. daily) will lead to enhanced protection of the skin barrier than current skin care practices and thus reduce the probability of developing AD.

The daily use of moisturizers in infants in our proposed study will likely not pose an increased risk beyond current standard usage. The main risk of the emollient would either be the development of an irritant contact dermatitis or rarely an allergic contact dermatitis to an emollient component. Theoretically, occlusive moisturizers could increase the risk of a skin infection, however this has not been seen in previous clinical studies of emollients in neonates. Moisturizer marketing campaigns currently promote the daily use of moisturizers in infants. Parents will have a choice of multiple legally marketed moisturizers for this study that are all freely available over-the-counter.

Parents in the intervention arm will select an emollient from the approved moisturizers list to use on their baby over the course of the study. These emollients do not pose any additional known risk to newborns or infants beyond current usage patterns in the community.

There is a risk of loss of confidentiality. The study team will take precautions to protect the confidentiality of participant information.

1.5.2 Potential Benefits

It is not known if there are benefits to using the preferred emollient for infants not at risk of developing AD (i.e. there is no family history of AD or allergies). Some studies show infants at high-risk for developing AD may benefit from emollient therapy, but these studies were small and need confirmation. While participation in this study may not provide direct benefits to participants, participation may help to understand how to prevent AD in infants.

2 STUDY OBJECTIVES

2.1 Study Objectives

2.1.1 Primary Objective

To assess the effectiveness of daily emollient therapy beginning in the first 2 months of life in reducing the cumulative incidence of AD at 24 months of age in a community-based setting.

2.1.2 Secondary Objectives

To determine whether an atopic family history and key early life exposures modify the effect of emollient therapy on atopic dermatitis.

To assess the effectiveness of emollient therapy on the development of reported allergic comorbidity symptoms such as food allergy and wheeze episodes.

2.2 Study Outcome Measures

2.2.1 Primary Outcome

The primary outcome will be an AD diagnosis made by the infant's primary healthcare provider by 27 months of age (cumulative incidence). A diagnosis will be recorded in the health record for each infant and these data will be extracted by PBRN research coordinators. Diagnosis guidelines and documentation will be introduced at an initial training session and provider compliance with this protocol will be monitored and reinforced by PBRN research coordinators. Any diagnosis of AD made by the trained provider during the first 27 months of life will be considered as having developed AD (i.e., cumulative incidence). Clinicians will be trained to use the American Academy of Dermatology (AAD) Consensus Criteria for diagnosing pediatric AD.[37] These criteria are a distillation of the original Hanifin-Rajka criteria with minor enhancements made by pediatric dermatologists to facilitate diagnosis in the very young. The recently-published AAD guidelines of care for AD recommend these criteria for the diagnosis of AD in the clinical setting.[38] The statistical analysis plan contains the full set of primary and secondary outcomes.

Table 1: AAD Consensus Criteria for diagnosing pediatric AD.

ESSENTIAL FEATURES
Must be present:
-Pruritus
-Eczema (acute, subacute, chronic)
-Typical morphology and age-specific patterns*
-Chronic or relapsing history
***Patterns include:**
1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions
IMPORTANT FEATURES
Seen in most cases, adding support to the diagnosis:
-Early age of onset
-Atopy-personal and/or family history
-Immunoglobulin E reactivity
-Xerosis

2.2.2 Secondary Outcomes

- Parental report of provider-diagnosed AD - This parental report of AD question has been validated previously by our group and was found to have adequate sensitivity and specificity during our trial planning activities.[39]

- AD as diagnosed by the Children's Eczema Questionnaire (CEQ) – The CEQ is a newly developed 2-question parental questionnaire based on the U.K. Working Party criteria.[40] This instrument will be used to capture dyads not evaluated by their provider or lost to follow-up (Appendix A).

- Parental report of sleep loss of the infant reported as average parental report of days per week of disrupted sleep in their infant (1 week recall) measured at 12 and 24 months.

- Any prescription topical medication use or over-the-counter hydrocortisone usage recorded by parent or recorded from records review by research coordinator at 24 months.

- Asthma risk questions from the modified Asthma Predictive Index (mAPI) that uses family history, atopic dermatitis, sensitization history, and wheezing episodes to predict the development of asthma measured by parental report.[41] This will be recorded as either high risk or low-risk at 12 and 24 months following mAPI criteria (Appendix B). Wheezing episodes will be assessed using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.

- Parental report of immediate food allergy symptoms – A general question regarding the development of red rash/hives, lip swelling, wheezing, abdominal pain, or vomiting that developed in the infant within two hours of eating a food.

- Parental report of a provider diagnosis of food allergy that was confirmed by prick testing or IgE blood test.

- One question global health status from the PROMIS Pediatric Global Health (PGH-7) instrument.[42] (Appendix C)

- In infants who develop AD, a logic model in our survey instrument will ask the following parental reported outcomes in the 12- and 24-month questionnaires:

    1. Time to onset of AD as measured by parental report of eczema age of onset.

    2. Time to onset of AD as measured by provider-recorded date of first diagnosis retrieved from record review of chart by research coordinator.

    3. AD symptom severity as reported by the Patient-Oriented Eczema Measure (POEM) instrument [43] (Appendix D).

    4. Parent-reported global severity of eczema assessment – mild, moderate, severe

    5. Infant Dermatology Quality of Life Instrument (IDQOL) – a validated 10-question questionnaire designed for children under 4 years of age [44] (Appendix E).

3 STUDY DESIGN

3.1 Study Design Overview

This is a pragmatic, multi-site, randomized community-based trial that will enroll dyads of a parent or guardian ("parent") and an infant who is up to 2 months old. Both high-risk infants (with family history of atopic disease) and average-risk infants (with no family history of atopic disease) will be eligible. Each dyad will be randomized to the intervention arm (daily emollient therapy) or the control arm (encouraged to adhere to current infant skin care guidelines without regular emollient use). Over the course of two years, 1,250 dyads will be enrolled in the trial with 625 dyads assigned to each study arm. It is anticipated that 2,500 dyads will be screened in order to reach the target enrollment.

Once randomized, dyads will participate in the study until the infant is 24 months of age (approximately two year study duration). Parents will complete a questionnaire at enrollment (prior to randomization) and follow-up annual questionnaires when the infant is 12 and 24 months old. Every three months of child's age (e.g., age 3 months, 6 months, 9 months, etc.), parents will be contacted via e-mail or SMS text message and asked to complete a quarterly survey, have an opportunity to update their contact information, report on adherence to study arm, be given messages about daily emollient use or general infant skin care guidelines and report adverse events and serious adverse events. Finally, two weeks after enrollment into the study, dyads in both arms will receive an e-mail or text message with a brief study message for both arms, with the intervention arm getting an additional message encouraging daily emollient use.

Total study duration will last for five years, with enrollment projected to be completed at the end of study year 2 and data collection projected to be completed at the end of study year 4. After completion of the screening and enrollment, participant-specific links to subsequent questionnaires will be sent by e-mail or SMS text message. Follow-up for incomplete questionnaires, unresponsive participants, as well as for individuals that did not have a valid e-mail address or phone that could not receive text messages may receive additional contact from the Clinical Coordinating Center (CCC).

3.2 Setting

This study will take place in 35 community-based primary care clinics located in four states in the United States: Colorado, North Carolina, Oregon, and Wisconsin. The community-based setting, combined with the multi-regional site selection, will increase the potential for racial and ethnic diversity representative of the U.S. population.

Prior to study implementation, the CCC and PBRN research coordinators will train participating clinic staff on methods for proper diagnosis of AD. PBRN research coordinators will ensure that staff and clinicians who join the study after initial training receive the training materials and complete a test.

3.3 Treatment Arms

There are two arms in the study- intervention and control. Both study arms will receive text messages and e-mail links providing general skin care educational material

throughout the study. This general skin care information includes information regarding the use of gentle cleansers, bathing safety tips and managing rash. All dyads will be reminded of their treatment arm every three months via electronic survey and e-mail. Both arms will be contacted at the same frequency. There are no evidence-based guidelines for frequency of bathing. Because bathing practices vary between families considerably, only general bathing tips will be provided to both groups.

3.3.1 Intervention Arm

Dyads assigned to the intervention arm will receive a study-approved emollient of their choice by mail at regular intervals throughout the study and instructed to use the emollient once-daily over the entire body. Parents may avoid the scalp, if needed. Quarterly reminders will be sent during the course of the study instructing parents on the daily use of the study emollient. In addition, the intervention group will receive general infant skin care information identical to the control group.

3.3.2 Control Arm

Dyads assigned to the control arm will be instructed to refrain from routine emollient use and only use emollients on an “as needed” basis if their baby develops dry skin. Like the intervention group, dyads in the control arm will also receive general infant skin care guidelines. Information in the control educational materials will include general infant skin care recommendations, such as bathing and rashes. The information in educational materials will be current standard of care for the topics included.

3.4 Rationale for Study Design Elements

3.4.1 Pragmatic Trial Design

It is now recognized that the results from traditional randomized controlled trials (RCTs) often do not generate the information necessary to properly inform health care guidelines or policy.[45] Trial participants often are not representative of the population in which the therapy will be implemented. This discrepancy can lead to well-tested therapies either not working, or to unexpected toxicities, when delivered in a real-world setting. Clinical trials, in contrast to traditional RCTs, are designed to address real-world clinical situations and provide results that are directly applicable to large populations.

3.4.2 Community-based Setting

A pragmatic trial using a community-based setting provides several advantages over a traditional RCT in the context of this study. First, by recruiting from primary care and pediatric clinics, we anticipate improved efficiency in enrollment and reduced loss-to-follow-up. Recently, a trial of emollient intervention for AD prevention from Australia could not be performed due to the study only enrolling 5% of their target sample size using a standard RCT approach.[50] Second, a community-based pragmatic trial design, unlike many RCTs performed in academic centers, allows for the results of the trial to be immediately generalizable to large populations. Trial design better mirrors how the intervention would be implemented in the general primary care community. By generating data regarding the *effectiveness* of this intervention in a community setting,

this trial design provides the best chance that the results of the trial will have the largest public health impact.

3.4.3 Clinician Training in AD Diagnosis

During the first two months of the funded project, all 25 community-based primary care study sites will undergo whole staff protocol training led by the CCC, PI and PBRN research coordinator. Training of all clinicians in performing the primary assessment occurs during this time using a competency-based training module with clinical assessment of AD. Clinicians will be trained in valid and standardized diagnosis using the American Academy of Dermatology (AAD) Consensus Criteria for diagnosing pediatric AD.[37]

3.4.4 Electronic-based Data Gathering

Parent-derived electronic data gathering greatly improves the overall efficiency of this trial.[49] Because of the size of the trial population and number of participating sites, traditional study visits with in-person assessments or exclusively over-the-phone contacts would be extremely costly. Electronic data gathering reduces the overall parent burden and clinic burden when participating in the study and greatly reduces the overall cost of the study data management.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Participant Inclusion Criteria

In order to be eligible to participate in this study all of the following criteria must be true for the dyad:

- Parent can provide signed and dated electronic informed consent form
- Parent is willing and able to comply with all study procedures for the duration of the study
- Parent is a primary caretaker of an infant 0 to 2 months of age
- Parent is 18 years of age or older at time of consent
- Parent can speak, read, and write in English or Spanish
- Parent has a valid e-mail address or phone that can receive text messages
- Parent has reliable access to the internet
- Infant is a patient of a participating Meta-LARC clinic site at the time of consent

4.2 Inclusion of Vulnerable Populations

4.2.1 Inclusion of Women

All adults, including women, who are at least 18 years of age and who meet inclusion/exclusion criteria will be eligible for study participation. There are no exclusion criteria with regards to gender of the infant.

4.2.2 Inclusion of Minorities

All members of racial and ethnic minority groups will be eligible for study participation and no participants will be excluded on the basis of race or ethnicity. All study materials will be provided in Spanish to include Spanish-speaking populations.

4.2.3 Inclusion of Children

Via parental consent, infants will be enrolled into this study based on the inclusion and exclusion criteria. In order to prevent AD, interventions directed at the earliest stages of life are needed since the majority of AD begins with the first two years of life. Child assent will not be obtained for this study, as children in the target age group upon enrollment are not developmentally able to provide assent. Informed consent will be obtained by one parent or legal guardian.

4.2.4 Inclusion of Neonates

The project will enroll dyads of parents and neonates/infants 0 to 2 months of age with the intervention targeted at parental skin care habits for the infant. Neonates of uncertain viability or nonviable neonates will not be included in this study. Viability will be determined by the fact that the infant is being seen at the outpatient clinic site (i.e. if the infant is a patient at the clinic, they are considered viable).

4.3 Participant Exclusion Criteria

A dyad who meets any of the following criteria will be excluded from participation in this study:

- Infant born at less than 25 weeks gestational age
- Infant has established eczema as diagnosed by the primary healthcare provider at clinic site of enrollment per parent report
- Infant has known adverse reaction to petrolatum-based emollients
- Infant has an immunodeficiency genetic syndrome such as Wiskott-Aldrich Syndrome or Severe Combined Immunodeficiency Syndrome
- Infant has extremely low birthweight (less than 1000g or 2.2 lbs [2 pounds 3 ounces] at birth)
- Infant has a sibling enrolled in the study
- Parent is unwilling or unable to comply with study procedures

4.4 Enrollment Procedures

4.4.1 Screening

Parent/infant dyads will be recruited from 35 PBRN-affiliated primary care offices in four states. Potential dyads will be informed of the study by clinic staff during any routine well-child visits or written communication up to 2 months of life. Clinics will encourage dyads to enroll prior to the child's first month of life to optimize the time that the skin barrier is protected. Eligible dyads may enroll in the study up until infant age 2 months (63 days). Clinic staff will provide interested parents with a tablet computer, a recruitment rack card or recruitment postcard with enrollment URL and QR code. Recruitment materials will be provided in clinic waiting rooms, clinic examination rooms, enrollment kiosks, through the mail, or via patient portal depending on clinic workflows during child or mother scheduled well visits. All screening and enrollment procedures will be performed online either in the office via computer tablet (e.g. iPad) or via internet-enabled phone or home computer. The electronic consenting process follows all IRB requirements for electronic consent.

Parents will be asked to review a study information sheet and consent to screening procedures. Those who agree will provide their primary contact information and answer a brief screening questionnaire to determine eligibility. Automated data checks will confirm eligibility via inclusion and exclusion criteria. Eligible dyads who wish to continue will be directed to review the consent form. Participants may complete the consenting procedure and enrollment questionnaire in clinic or at home. Potential participants lacking an e-mail address will be instructed to contact the research coordinator to proceed with screening and enrollment.

4.4.2 Additional Screening Procedures – Duke University

In addition to procedures described in section 4.4.1, Duke PBRN coordinators may provide recruitment materials to eligible dyads during routine well-child visits or may initiate phone, mail and/or portal outreach to families. All screening and enrollment procedures will continue online.

4.4.3 Additional Screening Procedures – Oregon Health & Science University

In addition to procedures described in section 4.4.1, and in response to impacts from the COVID-19 pandemic, Oregon PBRN coordinators may be granted access to the participating clinic's patient portal to initiate recruitment messages to potentially eligible families. All screening and enrollment procedures will continue online.

4.4.4 Consent and Enrollment

After reviewing the consent, parents will respond to a survey question asking whether they have any questions about the study. Those who have questions will be instructed to call a toll-free number and speak with a research coordinator to review all aspects of the project. The electronic data capture system (REDCap) will generate an e-mail to the study inbox notifying the research coordinator, who will contact the participant directly if a call is not received. After being informed of the study, parents will use the tablet, phone screen or computer mouse to electronically sign their name to the signature-enabled PDF consent form. After the participant has been determined eligible and given consent, eligible dyads will then be directed to complete the enrollment questionnaire and to provide additional contact information, including details for alternate contacts.

Upon completion of the enrollment questionnaire, dyads will be automatically assigned to a study arm using the randomization schedule.

4.4.5 Randomization

Upon randomization, REDCap will send notification, a PDF of informational materials, and a link to a welcome video via e-mail. Dyads randomized to the intervention arm will also complete an electronic survey to select an emollient from the approved list. Key information regarding treatment allocation (e.g. basics of emollient use or current infant skin care practices) will be submitted in the body of the e-mail, with further information available in printed study materials mailed to parents. For dyads that enroll with text message, the randomization notification and electronic survey to select an emollient will be sent via text message.

Dyads will be randomly allocated to the intervention or control arm using permuted block randomization stratified by clinic and parent-reported family history of AD. Stratifying by site will minimize bias from unmeasured clinic population characteristics while stratifying on family history will assure balance between treatment and control groups in regards to the underlying risk of AD, which has been shown to be approximately two-fold higher in this group.[53] In setting up the blocks for randomization we will use block sizes of eight and assigned at a 1:1 ratio to either the control or intervention arm. A randomization schedule will be created using a computer-based random number generator.

4.5 Blinding Procedures

Because of the nature of the intervention, it is not possible to keep dyads blinded to the intervention. Administering a placebo emollient would not be possible as there are no active ingredients in the emollient itself. Using an emollient that has no barrier improvement properties would likely be irritating to the skin and unethical to use on

infants. The lack of participant blinding is compensated for by the objective nature of the assessment (clinician-assessed AD) and by the final assessment being made by a blinded assessor.

Clinic staff at participating clinics will not be informed by study staff of participant enrollment or study arm, primarily to maintain blinding. There is a risk that parents may disclose their treatment group to clinic staff. Clinicians and clinic staff will direct participants to follow study skin care recommendations as described in study materials. Clinic staff should continue to treat skin-related diseases as they arise. After chart audit is completed on participants, clinicians will be asked which randomization arm they believe was assigned to individual participants.

PBRN research coordinators will be blinded and will be responsible for infants' health record review to collect the primary outcome from the participating clinics. If the family has disclosed the randomization status to the clinician, this information may appear in the health record. At completion of health record review, PBRN research coordinators will indicate which randomization arm they believe was assigned in order to measure whether the assessor became unblinded while reviewing the health record.

Maintaining integrity of randomization allocation and blinding is an important asset and will be maintained as a primary goal of the DCC. The principal investigator remains blinded during AE, SAE and UP assessment. DCC study personnel will be unblinded. CCC research assistants may become unblinded during conversations with participants during consent and enrollment, quarterly surveys, annual surveys, and in responding to incoming communications from participants.

4.6 Strategies for Recruitment and Retention

Regional clinics will utilize clinic workflows to identify eligible dyads as they present for scheduled well child visits or when mothers present for scheduled prenatal or postpartum visits. The typical structure will place a tablet computer in the waiting room, recruitment kiosk or exam room to initiate study procedures. Rack cards or recruitment postcards will be offered to families to review after the clinic visit or sent via mail or patient portal. Recruitment flyers will be placed in waiting rooms and exam rooms with enrollment URL and QR code. Front and back office clinical staff will direct parents to the tablet or recruitment materials to initiate screening and enrollment. Patient-focused recruitment videos will be made available to clinics for use in introducing the study to dyads.

Each PBRN will assign a research coordinator to support participant recruitment efforts at regional clinics. Research coordinators will meet regularly with clinic staff, either in person or over the phone, to keep clinic staff engaged in the study and help clinics meet their enrollment milestones. Research coordinators will also support clinics who encounter challenges with meeting the recruitment goal of two dyads per month through conducting small tests of workflow changes and clinical observations to identify opportunities for recruitment.

During approximately 24 months of study participation, parents will receive periodic study communications in multiple formats. Dyads will receive compensation (Table 2) to incentivize completion of questionnaires and to enhance participant retention. Dyads

randomized to the intervention group will receive 24 months' worth of emollient over the course of the study.

Table 2: Schedule of compensation

Infant Age	Compensation for Completion of:	Compensation Amount
0 to 2 months	Enrollment Questionnaire	$35
12 Months	12 Month Questionnaire	$50
24 Months	24 Month Questionnaire	$50
Total Study Compensation		$135

Although the primary study outcome is not dependent on information derived from questionnaires, maintaining contact with parents for the entire study duration is critical. At baseline, parents will be asked to provide alternate contacts. During quarterly contacts, parents will be asked to update contact information in order to minimize loss to follow-up. If a participant becomes unresponsive during the study, or a participant phone number or e-mail address becomes invalid, CCC research coordinators will reach out to alternate contacts and may coordinate with clinics to search for updated contact information in the health record.

Parents will receive study information primarily through electronic methods. Electronic communication and data gathering is a more efficient and cost-effective method of maintaining a longitudinal cohort than traditional mail/paper methods.[54] In addition, after enrollment, all dyads will receive a mailed welcome packet with study and compensation instructions, contact information and a study magnet.

4.7 Participant Withdrawal

Dyads may withdraw voluntarily from the study at any time upon request. To withdraw from the study, participants will be asked to contact the CCC by phone or e-mail to inform of their intention to withdraw and to state the reason for their withdrawal.

4.7.1 Reasons for Withdrawal

An investigator may terminate a dyad's participation in the study if any of the following occur:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would be contraindicated.
- The dyad meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. Participants that develop atopic dermatitis will not be withdrawn, as that is the primary outcome.

- Serious complications arise where continuation of treatment is deemed inappropriate or impossible.
- An infant is removed from custody of the participating parent.

4.7.2 Handling of Participant Withdrawals or Participant Discontinuation of Study Intervention

Parents who withdraw their dyad from study participation or whose participation is terminated by the investigator will be informed (at the time of initial informed consent) that the investigator will retain and analyze data already collected prior to the date of withdrawal or termination. Participants who withdraw will be asked for: 1) reason for withdrawal, and 2) whether the participant wishes to withdraw from the intervention only or from all components of the research study, including continued survey data collection and chart review. The importance of continued follow-up data collection will be explained to all participants who withdraw, including information about maintaining the integrity of research data and assessing safety and efficacy outcomes.

A withdrawal or termination will be reported to the IRB if the withdrawal or termination is related to an unanticipated problem involving risk to the dyad or serious adverse event.

Participants who withdraw or are terminated from the study will not be replaced with a new participant. The proposed dyad recruitment numbers account for attrition.

4.7.3 Lost to Follow Up

A participant will be considered lost to follow-up if they have no documentation in the electronic medical record of AD and they have no 2-year visit data available given appropriate time windows.

5 STUDY INTERVENTION

5.1 Rationale for Promotion of Specific Emollients

Studies in both healthy and diseased skin have shown that most oil-in-water emollients improve skin barrier function by providing the skin a protective lipid barrier.[55-64] A wealth of data show petrolatum-based emollients applied to the skin improve barrier function (TEWL and hydration), decreases the effects of skin irritants, and improve clinical outcomes.[23,65-72] While initial studies found emollient formulations with ceramides and specific lipid ratios improve the skin barrier in mice,[73] studies in humans have failed to demonstrate they are superior to simple petrolatum-based emollients.[23,70,74] A recent clinical study in children found a ceramide-dominant emollient did not provide superior clinical results when compared to Aquaphor (41% petrolatum).[23] Similar findings were found in a clinical study of hand eczema.[75] Given the lack of data supporting their use over low-cost alternatives, we have primarily included simple petrolatum-based emollients in the study.

Consistent with a pragmatic trial approach, parents will be allowed to select an emollient from a list of five emollients. We performed a survey of pediatric dermatologists (n=10) with a special interest in AD research, who confirmed that the emollients chosen for this trial are ones they found most effective in practice to prevent disease recurrence and that no one emollient is clinically superior. Emollients included in the trial:

1. Are petrolatum-based
2. Are widely available
3. Are of reasonable cost for daily use for 24 months
4. Parents will also be instructed that they can change emollients at any point during study participation, as long as they change to an emollient on the approved list.

5.2 Emollient Choices

During enrollment procedures, parents assigned to the intervention arm will be instructed to choose an emollient from a study-approved list. They will be instructed to apply full-body emollient once per day on their infant. The emollients that will be recommended for use are shown in Table 3.

Table 3. Emollient Acquisition

Emollient	Evidence supporting use
CeraVe ointment (replacement for Aquaphor*)	Refs. 56, 58
Petrolatum (e.g. Vaseline)	Refs. 68, 71
Cetaphil Cream	Ref. 63
CeraVe Cream	Ref. 64
Vanicream	none, pediatric derm recommended

** CeraVe Ointment contains similar percent petrolatum as Aquaphor (46.5% versus 41%) and does not contain lanolin and bisobolol, two potential sensitizers.*

We have received donations from all three sponsor companies to supply emollient options that will be provided to participants. Emollients will be provided directly to the DCC. Other emollients will be acquired using available research funds from the Department of Dermatology, if needed.

After completing the enrollment questionnaire, participants in the intervention arm will receive an e-mail with a survey link to select an emollient from the approved list, followed by a reminder SMS text message to check their e-mail if emollient is not selected. The dyad will be assigned CeraVe cream, the most popular emollient, if one is not selected within three business days of enrollment. Participants in the intervention arm will receive a six-month supply of emollient at enrollment, 6 months, 12 months, and 18 months. Dyads can request additional emollient supplies between scheduled shipments, and those requests will be entered into the study database for use in adherence monitoring.

IRB approval will be accomplished through IND and IDE as outlined from communication with the FDA (See Protocol Appendix G).

5.3 Formulation, Packaging, and Labeling

No special formulations, packaging, or labeling requirements will be needed as these emollients are currently available over-the-counter to the general population and will be used in a manner similar to current use in the general population.

5.4 Emollient Storage and Stability

No special storage or stability issues will be needed beyond manufacturers' recommendations. Emollients will be stored in locked cabinets within climate-controlled offices at the DCC prior to distribution. Participants will be asked to follow any recommendations on the product in regards to storage requirements. Emollient expiration dates will be checked prior to shipping and emollients that expire within six months of the shipment date will not be distributed. Emollient will be mailed within three business days of enrollment and receiving participant's mailing address.

5.5 Dosage, Preparation and Administration of Study Product

Parents in the intervention group will be asked to use a once-daily dose of the emollient, a frequency used currently in the general population on a regular basis.[34,35]

5.6 Accountability Procedures for the Study Product

Receipt of emollient shipped to dyads will be confirmed using e-mail. Dispensing and receipt of emollients will be tracked in the study database. Logs will be maintained of emollient brands, lot numbers, expiration dates, shipping dates and participant IDs to track distribution of products. The DCC will review inventory logs to monitor need to request additional batches of emollients. Adherence will be monitored via survey questions and used containers will not be collected by the study team. Parents will be instructed to discard unused emollient or continue using after the infant reaches 24 months of age.

5.7 Assessment of Participant Adherence with Study Product Administration

Participant compliance with daily emollient use (intervention) and general infant skin care guidelines (control) will be assessed through quarterly and annual surveys through 24 months. Pragmatic trial design principles de-emphasize adherence monitoring; however, because this is the first trial of its kind in this population, adherence will be assessed by parental report on quarterly surveys to gain further information on usage patterns. Additional requests for refills will be recorded to indicate adherence to study product administration. The methods used to enhance adherence to the emollient use fall within the scope of what would be feasible in routine practice.

5.8 Concomitant Medications/Treatments

No restrictions on concomitant medications will be placed. Participants may treat any skin condition or other medical condition with therapy deemed appropriate by their infant's healthcare provider.

5.9 Administration of Intervention

The intervention (promotion of emollient use) will be administered electronically. Participants in the intervention arm will receive a welcome packet and a welcome e-mail, which will have links to text and video educational materials, a list of the preferred emollients, and contact information for the study team, including for reporting skin product-related adverse events. Intervention arm participants at each quarterly survey will also receive reminders encouraging use of emollient. Participants in the control arm will receive a welcome packet and a welcome e-mail with current skin care recommendations and contact information for the study team to report skin product-related adverse events. All questionnaires and brief contacts will be delivered by SMS text message or e-mail, and compensation for study participation will be administered electronically. Table 4 corresponds to the timing of questionnaire administration and emollient resupply.

Table 4: Questionnaire administration and emollient resupply schedule.

	Arm																	
	Intervention									**Control**								
Infant Age (in months)	≤2	3	6	9	12	15	18	21	24	≤2	3	6	9	12	15	18	21	24
Questionnaire	X				X				X	X				X				X
Quarterly Contact		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Study payment	X				X				X	X				X				X
Emollient supply shipped	X		X		X		X		X									

6 STUDY SCHEDULE

Please note, the word “contact” will be used in place of “visit” as all study contacts will occur electronically and may occur outside of any patient visit to their provider.

6.1 Baseline

Screening Contact (Infant Age 0 to 2 Months)

The purpose of the screening contact is to determine eligibility for study participation. Clinic staff will direct parents of infants under 2 months old to REDCap to complete screening. Screening at participating clinics will occur via a tablet computer through interacting with the study screening survey. Parents who are unable to complete the screening contact in the office will be given a rack card at the clinic, via mail or via patient portal with a URL and QR code to access the screening online from a smartphone or home computer. The following activities will occur during the screening contact:

- Obtain and document electronic consent from potential participant with a screening consent form.
- Participant completes a brief screening questionnaire to determine eligibility based on inclusion/exclusion criteria.
- If eligible, participant will provide contact information of name, primary phone number and e-mail address, then proceed to consent.

The total time anticipated to complete the screening contact is 5 minutes. Potential participants who have questions about the study or who lack an e-mail address will be directed to a toll-free number to call the CCC staff and receive additional information and clinic staff will be instructed to direct all potential participant questions to the CCC staff.

Logic programmed into REDCap forms will confirm eligibility criteria, and DCC staff may review to confirm.

Enrollment/Randomization (Contact 1, Infant Age 0 to 2 Months)

Study participants must complete the screening contact and provide informed consent to proceed to the Enrollment Contact. The following will then occur in the order specified below:

a. Parents will be directed to an online consent form for the parent/infant dyad. The consent will be reviewed and participants will be asked whether they have questions to be discussed with research staff.
    a. Parents who have questions will be provided a toll-free number to call. Research staff will receive an automated e-mail from REDCap with an alert that a parent has questions. The research coordinator will respond to all study questions and interested parents will continue to consent.
b. The consent form will be signed online with an electronic signature. The electronic consent form will be available to download and print as a PDF document; and an electronic copy will be sent to the primary e-mail address

provided by the participant. Electronic copies will not be provided to those lacking an e-mail address.

c. After consent, parents will then be asked to complete the enrollment questionnaire online. Dyads will complete all study screening and enrollment procedures before they are considered enrolled into the trial. Enrollment questionnaire includes the following:

- Family history of allergies
- Home environment
- Skin care practices
- Demographics
- Contact information, including alternate contacts

Once dyads complete enrollment procedures, they will be randomized and will receive an e-mail with information about their treatment arm, a PDF of study information and a link to a welcome video. Dyads who are randomized to the intervention arm will be sent a link to a survey to choose from one of five approved emollients, and the emollient will be shipped to their designated address within three business days of receiving the participant's shipping address. Study payment and randomization arm-specific details will also be mailed to all enrolled participants within three business days of receiving the participant's shipping address. Dyads enrolling with only text message options will receive information about treatment arm via text message.

All procedures completed through randomization are considered 'baseline'. Parents who decline to provide consent to participate will be counted to determine refusal rates.

2 Week Followup, 14 days after enrollment

Two weeks after enrollment, a survey sent via e-mail or text message to the participant with instructions related to study arm. Dyads are asked whether they would like to talk with someone about randomization instructions and are directed to contact research staff via a toll-free number or e-mail. Research staff will initiate a phone call to the participant if the participant does not contact the researcher.

6.2 Intermediate Contacts

Contact 2, Infant Age 3 Months ± 14 days

Quarterly contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- Parental report of AD or eczema diagnosis by a clinician.
- Average daily usage of emollient
- Parental report of skin product-related adverse events and any serious adverse events
- Intervention group only: record emollient supply and ship resupply if requested

Contact 3, Infant Age 6 Months ± 14 days

Quarterly contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- Parental report of AD or eczema diagnosis by a clinician.
- Average daily usage of emollient
- Parental report of skin product-related adverse events and any serious adverse events
- Intervention group only: confirm preferred emollient and ship resupply

Contact 4, Infant Age 9 Months ± 14 days

Quarterly contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- Parental report of AD or eczema diagnosis by a clinician.
- Average daily usage of emollient
- Parental report of skin product-related adverse events and any serious adverse events
- Intervention group only: record emollient supply and ship resupply if requested

Contact 5, Infant Age 12 Months - 4 weeks + 12 weeks

12 month questionnaire contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- AD or eczema diagnosis by a clinician.
- Parental report of skin product-related adverse events and any serious adverse events
- Skin care practices, adherence to intervention/control instructions
- Parental report of sleep loss
- Medication history
- Modified Asthma Predictive Index (mAPI) and International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire
- Infant diet
- Food allergy questions, including parental report of clinician-diagnosed food allergies
- In infants who develop AD:
    - Parental report of AD age of onset
    - AD symptom severity using POEM
    - Parent-reported global severity of eczema
    - Infant Dermatology Quality of Life Instrument (IDQOL)
- Intervention group only: confirm preferred emollient and ship resupply

After the infant is 12 months of age, the health record will be reviewed by a blinded research coordinator to collect the following:

- Provider diagnosis of AD or eczema
- Medication history

- Provider diagnosis of hay fever/allergies, asthma, and/or food allergies
- Skin product-related adverse events
- Serious adverse events
- In infants who were diagnosed with AD/eczema:
    - Date of diagnosis
    - Severity
    - Prescribed medications for treatment of AD, eczema, or rash

Contact 6, Infant Age 15 Months ± 14 days

Quarterly contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- Parental report of AD or eczema diagnosis by a clinician.
- Average daily usage of emollient
- Parental report of skin product-related adverse events and any serious adverse events
- Intervention group only: record emollient supply and ship resupply if requested

Contact 7, Infant Age 18 Months ± 14 days

Quarterly contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- Parental report of AD or eczema diagnosis by a clinician.
- Average daily usage of emollient
- Parental report of skin product-related adverse events and any serious adverse events
- Intervention group only: confirm preferred emollient and ship resupply

Contact 8, Infant Age 21 Months ± 14 days

Quarterly contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- Parental report of AD or eczema diagnosis by a clinician.
- Average daily usage of emollient
- Parental report of skin product-related adverse events and any serious adverse events
- Intervention group only: record emollient supply and ship resupply if requested

Contact 9, Infant Age 24 Months - 4 weeks + 12 weeks

24 month questionnaire contact sent to parents by text message and/or e-mail.

- Confirm or update contact information.
- Confirm or update primary care clinic where infant receives care.
- AD or eczema diagnosis by a clinician.
- Skin product-related adverse events
- Serious adverse events
- Skin care practices, adherence to intervention/control instructions
- Parental report of sleep loss

- Prescription or over-the-counter topical medication use
- Modified Asthma Predictive Index (mAPI) and International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire
- Food allergy questions, including parental report of clinician-diagnosed food allergies
- In infants who develop AD:
    - Parental report of AD age of onset
    - AD symptom severity using POEM
    - Parent-reported global severity of eczema
    - Infant Dermatology Quality of Life Instrument (IDQOL)

6.3 Final Study Contact

Contact 10, Infant Age 24 Months + 90 days

Infant health record review by blinded research coordinator to record clinical assessments through 2-year well-child check (up to 27 months of age). Coordinator to collect the following:

- Primary Endpoint: Provider diagnosis of AD or eczema
    - Any diagnosis of eczema, atopic dermatitis, or atopic eczema at any visit
    - Any qualifiers like “probable” or “probable.” These will be coded as having atopic dermatitis for the primary analyses.
    - Date of first diagnosis
    - Treatment(s) used for AD- dose, frequency
- Secondary Endpoints from chart review
    - Date of first diagnosis of AD by clinician in chart
    - Approximate date of onset of symptoms if recorded (age of child in months)
    - Presence of wheeze and date of onset
    - Diagnosis of atopic comorbidities: asthma, allergic rhinitis, food allergy
    - Any allergy testing- skin prick tests or blood
- Medication history: Any skin-directed prescription therapies:
    - Antibacterial (e.g. mupirocin, bacitracin)
    - Anti-inflammatory (topical corticosteroids, topical calcineurin inhibitors, crisaborole)
    - Antifungals (e.g. ketoconazole, econazole, terbinafine)
    - Antivirals (e.g. acyclovir ointment)
    - Any oral antibiotics prescribed for any indication- name of antibiotic, duration indicated on prescription, and indication if stated
- Provider diagnosis of hay fever/allergies, asthma, and/or food allergies
- Gestational age
- Birth weight
- Adverse events
    - Only skin product-related adverse events mentioned in the clinical chart will be captured. Event start and stop dates (if known) will be recorded, outcome and treatments needed.
    - Any serious adverse events (SAEs), not only skin-related, will be captured

- In infants who were diagnosed with AD/eczema:
    - Date of diagnosis
    - Severity
    - Prescribed medications for treatment of AD, eczema, or rash

6.4 Post-Participation Study Contact

After participation in the study surveys has concluded, parents will be asked about willingness to participate in additional research:

- Willingness to continue in the cohort or other research
    - Preferred contact method

6.5 Withdrawal Contact

If a dyad withdraws early parents will be asked to provide the following information:

- Reason for withdrawal
- Components of the study from which they will withdraw participation (e.g. intervention only, intervention plus continued data collection)

7 STUDY PROCEDURES /EVALUATIONS

Questionnaires and data abstracted from the infant's health record comprise the majority of study procedures. No in-person study procedures will take place, though infant/parent dyads will complete well-child visits with their provider during the first 2 years of life as part of standard clinical care. Appendix I and Appendix J provide a schedule of events with an overview of the study schedule and procedures.

7.1 Study Procedures/Evaluations

- Questionnaires: quantitative, parent-reported data will be collected from questionnaires. Parents will complete questionnaires about their infant's health, AD symptoms or diagnosis, allergy symptoms or diagnosis, AD risk or family history, and other measures listed in Appendix F.

- Validated AD instruments: validated instruments which measure AD symptoms, severity, risk-factors, and impact of AD on quality of life (Appendix A-E) will be used in the questionnaires.

- Medication history: only information about skin-related medications and antibiotic use will be collected from parents and from the infant medical record. These medications may include topical over-the-counter and/or prescribed medications, as well as oral medications that are used to treat skin conditions (i.e. antibiotics or steroids).

- Health record abstraction: a health record abstraction conducted at 12 months and the final study contact will collect data about provider-diagnosis of AD and allergies, treatment of AD and skin-related diseases, and severity of AD.

8 ADVERSE EVENTS REPORTING

Adverse events (AEs) in this study will be identified (1) by parent report through responses the parent provides in electronic contacts (refer to section 5.4), selecting the link for reporting skin product-related AEs provided on the websites, (2) by parent report via phone or email contact to the CCC, and (3) by review of the infants' medical record through ages 27 months. AEs will be graded as to their expectedness and attribution by the principal investigator (unrelated, possibly, probably or definitely related to the protocol). Due to the nature and low risk of the intervention, only skin product- related adverse events in randomized infants will be actively captured by patient report at least quarterly. These skin product-related AEs may qualify as serious adverse events (SAEs) or Unanticipated Problems (UPs) and will be actively monitored and reported by the PI and study team on a daily basis. All SAEs, not just skin product-related, will also be captured by patient report quarterly.

Clinic chart audits through 27 months will record all skin product-related AEs and UPs and all SAEs (whether or not they are skin product-related) and will be reported according to the timelines specified in the MOOP and the DSMP.

8.1 Definitions

8.1.1 Adverse Event (AE)

Any untoward or undesirable, although not necessarily unexpected, event experienced by a human participant that may be a result of:

- The interventions and interactions in the research
- The collection of identifiable private information in the research
- An underlying disease, disorder, or condition of the participant that could be reasonably attributed to emollient use
- Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the participant

8.1.2 Serious Adverse Event (SAE)

Any AE that:

- Is fatal
- Is life-threatening
- Is persistent or significantly disabling or incapacitating
- Results in inpatient hospitalization or prolongation of hospitalization
- Results in psychological or emotional harm requiring treatment (not applicable in our population)
- Creates a persistent or significant disability
- Causes a congenital anomaly or birth defect (not applicable in our population)
- Results in a significant medical incident (considered to be a serious study related event because, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition)

8.1.3 Unanticipated Problem (UP)

Events that are not expected given the nature of the research procedures and the participant population being studied and suggest that the research places participants or others at a greater risk of harm or discomfort related to the research than was previously known or recognized. Harm to a participant need not occur for an event to be an unanticipated problem.

8.1.4 Deviation

A deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Operating Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations will be reported according to the timelines specified in the MOOP and the DSMP.

8.2 Reporting Adverse Events

All AEs, SAEs, and UPs will be documented on the appropriate adverse event questionnaire, entered into the REDCap database, and reported to the DCC as outlined below.

- All skin product-related AEs and all SAEs will be reported by participants in their surveys (at defined contacts) or by direct notification of study staff (through website links or by directly calling study phone number).
- All skin product-related AEs and all SAEs identified during chart audit will be entered into REDCap by PBRN research coordinators.

The DCC will evaluate each event and will determine reporting requirements. The DCC will report events to the Data and Safety Monitoring Board (DSMB) according to the following timeframes:

- All SAEs and UPs that require expedited reporting (SAEs that are deemed related and unexpected, all UPs) will be reported to the IRB within 48 hours of the time the PI learns of the event.
- Only SAEs provided to the study team will be reported.
- All other AEs will be reported to the DSMB semi-annually.
- Summary AE and SAE reports will also be submitted to the IRB at least annually.

9 STUDY OVERSIGHT

In addition to the PI, Clinical Coordinating Center, and Data Coordinating Center having responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) created with the NIAMS. The DSMB will review reports bi-annually, starting 6 months after the first patient enrolls, to assess safety, study progress, and data integrity for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of a NIAMS-approved Data and Safety Monitoring Plan (DSMP) with oversight by NCR (formerly KAI) Research, the NIAMS Collaborator. The DSMP will outline the charge to the NIAMS-approved monitoring body and is intended to be a living document to be modified at any time if any processes or procedures were to change.

The PI will routinely report ongoing study activities with emphasis on data integrity and participant safety issues, such as SAEs and other events requiring expedited reporting.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

The primary hypothesis of this study is that an intervention to encourage parents to apply daily emollients will reduce the cumulative incidence of AD at two years of age. We will test the hypothesis that the relative risk of AD for the treatment versus control group is not equal to one.

10.2 Study Outcomes

10.2.1 Primary outcome

The primary outcome will be any AD diagnosis made by the child's healthcare provider by 27 months of age (cumulative incidence or cumulative proportion) using standard crtieria.[76] (See Section 2.2)

10.2.2 Key Secondary Endpoints

The key secondary endpoints include: AD diagnosis using parental report, need for prescription anti-inflammatory cream for the skin, incidence of skin care-related adverse events and skin infection, tolerability of the intervention, number and type of yearly wheezing episodes that predict asthma risk [41] and immediate type I hypersensitivity symptoms related to foods. In children who develop AD, the severity of symptoms (POEM) and the impact on infant quality of life (IDQOL) will be measured.[43,44] The Statistical Analysis Plan contains a full list of secondary outcomes with supporting references.

10.3 Power and sample size calculations

10.3.1 Power and sample size

Table 6. Power to detect plausible interactions in exploratory analyses (Aim 2).

Risk factor	AD risk	Prev-alence	Tx effect if RF+	Tx effect if RF-	Tx effect DIFF	Power at α = 0.1
Family hx of atopy	2.0	0.50	0.63	0.83	-0.20	0.48
			0.60	0.90	-0.30	0.56
			0.57	0.97	-0.40	0.64
High humidity	0.8	0.44	0.82	0.62	0.20	0.40
			0.89	0.58	0.30	0.52
			0.95	0.54	0.40	0.65
Cat owner	1.0	0.30	0.84	0.64	0.20	0.36
			0.91	0.61	0.30	0.48
			0.98	0.58	0.40	0.60
Dog owner	0.7	0.37	0.84	0.64	0.20	0.36
			0.91	0.61	0.30	0.46
			0.98	0.58	0.40	0.59

10.3.2 Primary Outcome

For the purpose of the primary analysis, we will include a sufficient number of babies in a 1:1 ratio for the two study arms to provide an overall type I error rate of 0.05 and 80% power to detect a 30% relative reduction in cumulative incidence over 2 years (also known as incidence proportion) of AD (RR=0.7). From our planning grant, we estimated the baseline cumulative incidence of AD in this age group and target clinics at 24% at age 2, The trials in high-risk populations of daily vs no emollient have shown reductions of 50%, we assumed a more conservative 30% reduction to 16.8%. Using the O'Brien-Fleming group sequential spending function approach, a total of 982 infants (491 per arm) are required to detect this difference in proportions. Allowing for an approximate 20% loss to follow-up, we plan to enroll **1,250** dyads (625 per arm). Sample size calculations were performed using Stat/IC version 16.1.

10.3.3 Power and sample size for detecting effect modifications

To determine our power to detect significant effect size differences stratified by various baseline variables (interaction) such as sex, race or ethnicity, atopic family history, climate, and pet ownership, we generated plausible 2x2 tables of risk factors (RFs) and AD for each treatment group that would yield absolute differences in the treatment effect of 0.2, 0.3, and 0.4, taking into consideration the study sample size, overall projected AD and treatment effect, previously published risk of AD for the RF, and prevalence of the RF. We simulated 500 replicates of each scenario using the binomial probabilities from the 2x2 tables and tested for significance of the interaction in a log-binomial (relative risk) model as described below. The power estimates in Table 6 are the proportion of simulated datasets in which the null hypothesis was appropriately rejected.

10.4 Statistical analyses

10.4.1 Analysis of Primary Endpoint

For our primary analysis, we will contrast the risk of diagnosed AD by two years of age for the intervention versus control groups under an intention-to-treat (ITT) assumption, where all subjects will be analyzed according to the group to which they were allocated regardless of adherence or group cross-over, and missing outcome values will be multiply imputed using the expectation-maximization (EM) algorithm.[78] Model: We will use logistic regression with a treatment variable (intervention=1, control=0) and perform a two-tailed likelihood ratio test of the treatment effect at the overall 0.05 level of significance using an O'Brien-Fleming critical boundary to accommodate one planned interim analysis. Because randomization will have been stratified by clinic and family history of AD in a first-degree relative (yes/no), we will include these variables to avoid overestimation of the p-value.[79,80] We will estimate the absolute and relative differences between groups as the (1) difference and (2) ratio, respectively, of the average conditional predicted risk for intervention versus controls from the logistic model, calculating standard errors and 95% confidence intervals using the delta method. We will use an inclusive strategy to select variables when imputing the missing outcomes [77,81] using intervention status and clinic along with parent-reported provider diagnosis, risk factors, and emollient use from electronic survey and text responses, as well as interaction terms found to be significant in Aim 2 (below).

10.4.2 Effect modification of primary endpoint

We will examine potential modification of the intervention effect by sex (consistent with NIH guidelines), race or ethnicity, atopic family history, climate, and pet ownership by creating separate logistic regression models under multiple imputation that include the variable of interest with intervention status and an interaction term, adjusting for stratification variables. Multiple imputation will be performed as above with the interaction term included in the imputation step. We will test for significance of the interaction term with a two-sided Wald test at the 0.1 level. A level of 0.1 was used because of the exploratory nature of this aim that will be solely used to guide future research and due to the impracticality of fully powering this secondary analysis.

10.4.3 Secondary analyses of primary endpoint

As a sensitivity analysis, we will perform a complete-case analysis using only subjects who have non-missing outcome data in a logistic regression model adjusting for stratification variables as well as covariates that we find to be associated with missing AD status.[78] The effect of emollient use will be evaluated with a model similar to the primary analysis, but substituting an indicator of regular reported emollient use (≥3 days per week) for intervention allocation. In a separate model, we will include a variable for bathing frequency. In the likely case that bathing and emollient use frequency are associated, we will create and test a combined categorical variable. We will return to the primary intervention-effect model and consider additional covariates previously found or suspected to be associated with AD, such as climate, season of birth, pet ownership, bathing frequency, and characteristics of the living environment using a change-in-estimate approach.[83] Finally, we will compare clinic-stratified intervention effects on the primary AD outcome and test their equality with a Breslow-Day test; the purpose is to identify 'large' differences where further investigation into potential protocol deviations or other factors may be warranted, and these results will be interpreted with caution.

10.4.4 Analysis of Key Secondary Endpoints

To test the hypothesis that emollient use delays onset of AD, we will compare time to onset using child's age in months with discrete time-to-event methods.[84] Time to AD onset will be defined in two ways, as (1) parental report of age of eczema onset and (2) age at first diagnosis recorded in patient chart. Censoring will occur at the date of last parental report or last visit recorded in the patient chart. We will also compare the intervention and control groups with respect to conditions and symptoms that include the need for topical therapy, asthma, food allergy symptoms, and dichotomized disease severity measures as binary measures, sleep loss days as counts, and AD severity scores (POEM and IDQOL) as continuous measures. We will test for differences using logistic, Poisson, or linear regression, adjusting for stratification variables. The incidence of adverse events at two years of age will also be compared between the treatment and control groups with a two-tailed chi-square test at the 0.05 level of significance.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives of NIAMS and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

12.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. A description of possible risks and benefits of study participation will be provided to families. An IRB-approved consent form describing in detail the study procedures and risks will be reviewed electronically and made available to the participant. The CCC will be available via toll-free phone number to explain the research study to the participant and answer any questions that may arise. The participant will electronically sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants may withdraw consent at any time throughout the course of the study. An electronic copy of the signed informed consent document will be available to download and will be e-mailed to participants for their records. Participants will be informed that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the research record.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and medical chart abstractions must be reviewed by the CCC and DCC staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events will be reviewed by the PI.

13.2 Data Capture Methods

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Data will be collected directly from parents using web-based surveys. PBRN research coordinators will perform health record reviews of enrolled infants at 24 months and send data to the CCC to enter directly into the REDCap database. In both cases, the case report forms will serve as source documentation. The DCC will monitor for timely entry of data and maintain a study calendar.

13.3 Types of Data

The following types of data will be collected over the course of the study:

- Questionnaire responses: electronic surveys will allow parents to enter data directly into a REDCap database. If necessary, DCC staff may contact parents to answer survey questions over the phone and will enter responses into REDCap.
- Health record review: research coordinators will perform health record review at infant age 27 months to see if an AD diagnosis has been made by the primary care provider, as well as other clinical data of interest.
- Current participant contact information
- Participant contacts and contact attempts
- Emollient preference and tracking
- Participant compensation
- Safety data: Safety data will be stored in REDCap with other study data.
- Missing Data

The study's approach to missing data follows the recommendations of the National Research Council of the prevention and treatment of missing data in clinical trials.[83] Specifically, we will use the following methods to prevent missing data and account for it in the analyses:

- Participants will be informed at the time of consent the importance of remaining in the study and providing reasons for withdrawal if needed

- Participant retention methods including text messaging and medical record review
- Key covariates will be collected at baseline regardless of intervention arm
- Missing data are addressed in our statistical analyses using state-of-the-art procedures like multiple imputation procedures and use of sensitivity analyses

13.4 Performance Monitoring

The DCC will present regular reports to the CCC and PBRN directors. These include:

- Monthly recruitment reports: reports of the number of dyads screened, enrolled, screen-failed, and randomized by month and by PBRN, as well as average randomized per month.
- Annual committee reports: reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical site, will be provided semi-annually to the Steering Committee.
- Semi-annual Safety Monitor reports: every report includes adverse events, patient recruitment, retention, baseline patient characteristics, center performance, timeliness of data submission and protocol adherence, withdrawals (in addition to safety and efficacy data). Data will be reported by clinic.

13.5 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIAMS. These documents may be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14 LITERATURE REFERENCES

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