Statistical Analysis Plan (SAP): Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE)

i. Administrative information

i.1. Version Information

Trial full title	Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE)
Trial short title	CASCADE
NIAMS grant number	R01 AR071057
Unique protocol id	00106351 (University of Utah IRB)
ClinicalTrials.gov registration	NCT03409367
SAP version	3.0
SAP version date	April 18, 2023
Senior trial statistician	Jodi Lapidus, PhD
Trial statisticians	Katrina L. Ramsey, MPH Jean Hiebert Larson, MS
SAP associated with protocol version	13 (06Jun2021)
Trial principal investigator	Eric Simpson

i.2. Revision History

Version 1.1

Justification: Edit plan submitted with funding proposal

Timing: Before analysis, study in progress

Revisions

- Reorganization of text for clarity
- Greater detail provided of variable definitions
- Secondary analysis of ceramide-containing emollients added in response to emerging efficacy evidence

Version 2.0

Justification: Recommendation of DSMB

Timing: Before analysis, study in progress, enrollment complete

Revisions

- Eliminate interim analysis. Revise sample size calculation without alpha spending.
- Add secondary outcome of skin infections (previously appeared in table but not text)
- Add exploratory analyses of bathing and caesarean births as effect modifiers
- Add sensitivity analyses of COVID-19 pandemic effects of potentially changing prevalence of (a) primary outcome and (b) respiratory syncytial virus (RSV) over time.

Version 3.0

Justification: Clarifications in response to questions raised during chart reviews

Timing: Before analysis, study in progress, enrollment complete (April 2023)

Revisions

1. Remove secondary outcome of AD diagnosis by any method (chart, parent report, instruments). Instead, analyze competing definitions using multivariate methods.
2. Add secondary endpoint of cumulative incidence of AD at 18 months. During chart audits (ongoing), research staff have noted that many children have visits in this window who may be missing a visit in the 24-month window.
3. For skin infection secondary endpoints, separate documented physician diagnosis from topical antibiotic prescription.
4. Add pooled logistic regression as an analytic approach for time to diagnosis.

i.3. Signatures

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ii. List of Abbreviations

AD	Atopic Dermatitis
AE	Adverse Event/Adverse Experience
CRF	Case Report Form

DSMB	Data and Safety Monitoring Board
IRB	Institutional Review Board
NIAMS	National Institute of Arthritis, Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
PBRN	Practice-based Research Network
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan

iii. Contents

1. Introduction: Background and Aims

Atopic dermatitis (AD) affects over 9 million children in the U.S. and ranks first among all skin conditions in global disability burden. Atopic dermatitis often heralds the development of several comorbidities including asthma, food allergy, skin infections and neurodevelopmental disorders. Because of the significant socioeconomic impact of atopic dermatitis and its effect on the quality of life of children and families, there have been decades of research focused on prevention with limited success. Recent advances in cutaneous biology identify epidermal defects and skin barrier dysfunction to be the key initiators of atopic dermatitis and possibly allergic sensitization. Our central hypothesis is that emollient therapy from birth can prevent the development of atopic dermatitis. The current trial has the following specific aims:

Aim 1: Perform a community-based pragmatic randomized controlled trial investigating whether daily full-body emollient application starting in the first 2 months of life prevents atopic dermatitis in a real-world setting.

Aim 2: As an exploratory aim, determine whether a family history of allergic disease and key early life exposures such as pet ownership modify the preventive effect of emollient therapy on atopic dermatitis.

Additional sub-aims include estimating the effect of emollient therapy on age of onset of AD, disease severity, and symptoms predictive of allergic disease further described below.

2. Study Methods

2.1. Trial Design

This study is a parallel-arm pragmatic randomized-control trial. Dyads of a parent or legal guardian ("parent") and a healthy infant ages 0 to 2 months will be enrolled and followed until age 24

months. Intervention dyads will receive specific instructions to apply full-body lipid-rich emollient daily to infants, plus routine skin care advice, and will receive an emollient of their choice mailed to them during study participation. The control group will receive general skin care advice only. Both groups will receive web-based and text message reminders to follow protocol instructions based on their group allocation until the infant reaches 24 months of age.

2.2. Randomization and Blinding

Participants are recruited from primary care practices participating in a consortium of practice-based research networks. Screening occurs through an online instrument hosted on REDCap. After passing screening and giving informed consent to participate in either arm, participants are randomized using a list embedded in REDCap. The randomization list was generated by study statisticians. Allocation is in 1:1 ratio stratified by primary care clinic, to assure balance at each location, as well as history of atopic disease in a first-degree family member[1]. Family history of atopy confers an approximate twofold risk of developing AD and may influence participation, adherence and retention as well, so it is important for the two study arms to be balanced on this risk factor.

Neither clinic staff (including primary providers) nor study personnel involved in chart review and analysis are informed of treatment assignment and uninformative labels (e.g. "A" and "B") will be used for the two arms when needed. Study participants are informed that it is not currently known which arm is better for skincare.

In recruitment materials, participants must be willing to be randomized to either arm. Intervention materials provide instructions specific to the randomization arm. Primary care clinicians will be asked to evaluate and document AD status at each well child visit through two years of age without knowledge of intervention status. Study personnel involved in chart review will not have access to participants' arm assignment, and during analysis, we will use generic labels for the two arms ("A," "B") until evaluation of the primary outcomes is completed, and whenever practical thereafter. Study personnel conducting chart review will be asked whether they became unblinded during the audit process.

2.3. Sample Size and Recruitment Duration

1,250 parent/infant dyads (625 per arm) will be enrolled from 25 community-based family medicine and pediatric practices in four states (Oregon, Colorado, Wisconsin, and North Carolina). All parents/legal guardians, including males and females 18 years of age and older who meet inclusion/exclusion criteria are eligible for study participation. Recruitment is expected to take place over the course of 31 months; the time from start of recruitment until final two-year follow-up on all subjects is five years.

Power for Aim 1. For the purpose of the primary analysis, we 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 of AD by two years of age (RR=0.7). In our planning grant, we determined the baseline cumulative incidence of AD in this age group and target clinics at 24%, which is consistent with recent population-based 2-year prevalence in the U.K.[1] Because our trials in high-risk populations of daily vs no emollient have shown reductions of 50%, we assume a more conservative 30% reduction to 16.8%. Using a test of two proportions, a total of 982 babies (491 per arm) are required to detect this difference. Allowing for an approximate 20%

[1] The screening questionnaire includes the question "Has at least one of your baby's blood-related PARENTS, BROTHERS OR SISTERS ever been diagnosed with asthma, eczema (atopic dermatitis) or hay fever (seasonal allergies)?" Strata are split at "Yes" responses vs. "No, or don't know."

loss to follow-up, we plan to enroll 1,250 babies (625 per arm). Sample size calculations were performed using Stata/IC version 16.1.

Power for Aim 2. To determine our power to detect significant interactions, 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 1 are the proportion of simulated datasets in which the null hypothesis was appropriately rejected.

Table 1. Power to detect plausible interactions in exploratory analyses.

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

2.4. Statistical Testing Framework

All statistical tests will be conducted as two-sided tests of inequality. For example, as our primary analysis, we will test the hypothesis that the ratio of the intervention:control proportions, a relative risk (RR) measure, is significantly smaller than 1 with a two-sided test: **RR ≠ 1 vs RR= 1**.

2.5. Timing of Final Analysis

The final analysis will take place after all chart reviews have been completed for the 24-month time point. This will occur after the three-month window closes for the youngest participant's second birthday.

2.6. Timing of Outcome Assessments

Endpoints are assessed briefly at 3-month intervals and in depth at 12 and 24 months of age. These include diagnosed AD, severity of symptoms, and development of potentially related conditions, such as allergies.

Table 2. Timing of assessments

Assessment	Child age	Window
Screening	≤ 2 months	0-9 weeks
Contact 1	≤ 2 months	0-9 weeks
Contact 2	3 months	± 14 days
Contact 3	6 months	± 14 days
Contact 4	9 months	± 14 days
Contact 5	12 months	-4 weeks + 12 weeks
Contact 6	15 months	± 14 days
Contact 7	18 months	± 14 days
Contact 8	21 months	± 14 days
Contact 9	24 months	-4 weeks + 12 weeks
Final Contact	24 months chart audit	Through 27 months of age

2.7. Study Schema

Parentheses (•) indicate that a measure applies to a subset of participants, e.g. intervention arm only, or only children with diagnosed AD.

Table 3. Study schema

Schedule of events		Screening	Contact 1	Contact 2	Contact 3	Contact 4	Contact 5	Contact 6	Contact 7	Contact 8	Contact 9
Child age (months)		≤ 2	≤ 2	3	6	9	12	15	18	21	24
Procedures											
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						•				•
	UK Working Party						•				•
	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						•				•

3. Statistical Principles

3.1. Level of Statistical Significance

In the primary analysis, use a type I error rate of 0.05. Secondary outcomes will be considered significant at α=0.05 and exploratory analyses at α=0.1. All tests will be two-tailed.

3.2. Adjustment for Multiplicity

To address type 1 error, we have specified a single primary outcome and provided detailed plans for secondary and exploratory analyses, many of which have correlated outcomes because they address alternative definitions of the same endpoint, or because they arise from a common cause. We plan to make all findings available with sufficient detail for readers to perform adjustments to a different false discovery rate if needed.

3.3. Confidence Intervals

Estimates will be reported with 95% confidence intervals.

3.4. Adherence

Participants in the intervention arm receive instructions to apply emollient daily, while those in the control arm are asked to refrain from emollient use. Frequency of emollient use, measured in days per week, is assessed for participants in both arms at each of the quarterly contacts from when the child is 3 months old to 24 months old. Participants are reminded of instructions per treatment arm at each quarterly and annual contact. Frequency of emollient use will be analysed as described in section 5 below.

3.5. Protocol Deviations

A deviation is any departure from the defined procedures as outlined in the study protocol that is not prospectively approved by the IRB. Deviations are unplanned and/or unintentional events.

Deviations will be assessed by the PI, then reported to the IRB, DSMB and the NIAMS.

Descriptions of all protocol deviations are included in bi-annual DSMB meetings, and are presented in both the open and closed reports.

3.6. Analysis Populations

The **Intention-to-Treat (ITT) Population** will contain all randomized participants. Missing outcomes will be multiply imputed to reduce bias without exaggerating precision per recommendations by Little and Yau for longitudinal studies[3].

The **Complete Case Population** will include the subset of participants with non-missing primary outcomes.

The **Per-Protocol Population** will assign participants who report emollient use to the intervention arm (regardless of randomization), and those who report no emollient use to the control arm. This dataset will be used to estimate the relationship between frequency of emollient use and AD.

The **Safety Population** includes all randomized participants. Safety outcomes are reviewed regularly by the DSMB.

The **AD Population** includes children with diagnosed AD (chart review).

4. Trial Population

4.1. Screening Data

We will prepare a flow chart of the numbers of interested individuals who are not eligible or choose not to participate based on the criteria detailed in the following sections and listed below in order of appearance on screening tools:

Language preference (English/Spanish)
PBRN (based on clinic)
Contact information provided (Email / Text-capable phone number / *Neither* email *nor* text-capable phone)
Are you a parent or guardian with custody of a baby that is less than 2 months old (about 9 weeks)?
Are you 18 years or older?
Do you have convenient access to the internet?
Did your baby weigh MORE than 2.2 pounds (2 pounds, 3 ounces or 1,000 grams) at birth?
Was your baby born more than 3 months early?
Has YOUR BABY been diagnosed with eczema or atopic dermatitis by a medical provider?
Has your baby been diagnosed with an immunodeficiency genetic syndrome, such as Wiskott-Aldrich Syndrome or Severe Combined Immunodeficiency Syndrome?
Do you have another child enrolled in the CASCADE study?
Declines to participate

We will capture all criteria that potential participants fail to meet. For the first three items (PBRN, language, and preferred contact modality) we will compare participants and non-participants. The remaining items relate to exclusion criteria and by definition will not describe participants. These data will be discussed within the context of different recruitment methods at each site within PBRNs.

4.2. Eligibility Criteria

The study will **include** dyads of parents and infants who meet the following criteria:

1. Parent can provide electronic signed and dated informed consent form.
1. Parent is willing and able to comply with all study procedures for the duration of the study.
2. Parent is a primary caretaker of an infant 0 to 2 months of age.
3. Parent is 18 years of age or older at time of consent.

4. Parent can speak, read, and write in English or Spanish.
5. Parent has a valid email address or phone that can receive text messages.
6. Parent has reliable access to the internet.
7. Infant is a patient at a participating Meta-LARC clinic site at the time of consent.

The study will **exclude** any dyad who meets any of the following criteria from participation:

8. Infant was born at less than 25 weeks gestational age.
9. Infant has established eczema as diagnosed by the primary healthcare provider at clinic site of enrollment per parent report.
10. Infant has known adverse reaction to petrolatum-based emollients.
11. Infant has an immunodeficiency genetic syndrome such as Wiskott-Aldrich Syndrome or Severe Combined Immunodeficiency Syndrome.
12. Infant has extremely low birth weight (less than 1000g or 2.2 lbs at birth).
13. Infant has a sibling enrolled in the study.
14. Parent is unwilling or unable to comply with study procedures.

4.3. Withdrawal and Follow-Up

This study has nine participant contacts, of which three (baseline, 12 months, and 24 months) are long-form questionnaires and six (at 3, 6, 9, 15, 18, and 21 months) are short responses. At each time point, we will tabulate three categories:

- Responses, including partial responses
- Missed contacts, meaning that a later response exists
- Withdrawals and losses to follow-up, where participants either inform the research team that they will not participate further, are considered lost to follow-up meaning there is no documentation in the electronic medical record and they have no 2-year visit data available given appropriate time windows, or cannot be contacted and no later contacts exist

When participants withdraw, they may give permission to include them in the final chart review to ascertain AD diagnoses. These participants would lack follow-up survey data but be included in the final analysis of provider-diagnosed AD. The general CONSORT diagram to be populated with screening and inclusion numbers for the ITT population in the final analysis is included as Figure 2.

Within each arm, we will calculate the percentage of randomized participants at each step for each of those categories. An outline of this tabulation is provided as Figure 3.

As described in our approach to missing data in the primary analysis, we will compare loss to follow up in the intervention versus control arms with an indicator of missingness at each time point. We will test for a study arm x time interaction in a population-averaged model with missingness as a binary dependent variable. These findings will inform our approach to imputing missing observations, including outcomes.

4.4. Descriptive Statistics

We will tabulate variables, including baseline characteristics, as detailed in Table 1.

5. Analysis

5.1. Statistical Hypotheses and Outcome Definitions

1. Our primary hypothesis is that the intervention will result in significantly **lower cumulative incidence of provider-diagnosed AD by age 24 months**.

After two years of follow-up, we will calculate the proportions of children diagnosed with AD by trained primary care providers in the intervention and control arms. Clinicians will be trained in pediatric AD standard diagnosis criteria.[4] As our primary analysis, we will test the hypothesis that the ratio of the intervention:control proportions, a relative risk (RR) measure, is significantly smaller than 1 with a two-sided test: **RR ≠ 1 vs RR= 1**. This analysis will be conducted in an intention-to-treat (ITT) analysis dataset of all randomized participants with multiple imputation for missing outcomes.

Provider-diagnosed AD, the current gold standard, will be recorded during chart abstraction and referred to as **GS-AD**. The case report form (CRF) includes a question:

> Was there a diagnosis of AD (includes eczema, atopic eczema, atopic dermatitis, and neurodermatitis)?

with forced choice responses:

> 1, Yes
> 0, No / No documentation
> 2, Not sure / Possible - AD diagnosis is not confirmed

The CRF further elaborates:

> To check "Yes", there must be an official diagnosis from a provider. If a provider is considering eczema as a possibility, or if a parent thinks the child has eczema, mark "Not Sure/Possible" and provide verbatim description from the medical record. Choose "Not sure/Possible" if there is some evidence of eczema but no official diagnosis.

All "not sure/possible" records and their explanatory notes will be reviewed by the principal investigator or dermatology physician co-investigators under blinding before the dataset is locked for analysis. Fields describing the presence and date of onset of similar or comorbid conditions--such as candida of the skin, impetigo, and molluscum--are part of this record. Parent responses to the Childhood Eczema Questionnaire[5,6] (CEQ) (see item 2c below) will also be available for review during this determination.

After this review, any child with a "Yes" response or adjudicated as probable AD by physician reviewers will be considered to have AD and the outcome variable will be set to equal 1. "No" and "Not sure" responses adjudicated as not probable AD will be considered not AD and the outcome will be set to 0.

We will test additional secondary hypotheses comparing the intervention arm to controls with two-sided inference tests. In all of the items below, "I don't know" responses will be treated as missing:

2. Lower cumulative incidence of AD at 24 months by alternative diagnosis definitions, namely:

   a) **Parent report (PR-AD)** of provider diagnosis[7], as a yes response to the following at any time during follow-up:

      > Over the past 12 months, has a healthcare provider said your child has eczema or atopic dermatitis?

   b) Diagnosis by the **UK Working Party criteria**[8] **(UK-AD)** at any time during follow-up, defined as a yes response to dry skin and a rash that causes itching, i.e.:

      > Does your child have, or has your child had, a red rash or eczema which can come and go?

Has this red rash or eczema ever caused any itching, scratching, or rubbing? (Note: Even a small amount counts)

Along with responses as follows (note that responses can be given at different data collection time points):

- [at least one selected] Select all of the areas where the red rash or eczema has been in the past year:
  Cheeks
  Around the eyes, ears, scalp, forehead, or neck
  Folds (creases) of elbows or behind the knees
  Wrist or ankle
  Outer arms/ legs
  Trunk
- [at least one yes] Has at least one of your baby's blood-related PARENTS, BROTHERS OR SISTERS ever been diagnosed with asthma, or hay fever (seasonal allergies)?
  Has your child ever been diagnosed with asthma by a healthcare provider?
  Has your child ever been diagnosed with hay fever or springtime allergies by a healthcare provider?
  Has your child ever been diagnosed with a food allergy by a health care provider?
- [Yes] Does your child have dry skin?

Note that the published version includes food allergy in first degree relative, which is not collected in this study.

c) Diagnosis by validated multi-item **Childhood Eczema Questionnaire (CEQ-AD)** completed by parent[5,6], if yes responses to all of the following three questions at any time during follow-up:

Does your child have, or has your child had, a red rash or eczema which can come and go?

Has this red rash or eczema ever caused any itching, scratching, or rubbing? (Note: Even a small amount counts)

Has this red rash/eczema affected any of the following areas during the last week: around the eyes, ears, scalp, cheeks, forehead, neck, trunk, folds of the elbows/behind the knees, wrist or ankle, outer arms/legs?

3. Lower cumulative incidence of AD at earlier time points, namely
   a) 12 months
   b) 18 months
4. Lower cumulative incidence of AD requiring prescription or over-the-counter therapies at 24 months:
   a) Clinically-significant (severe) AD (**CS1-AD**): A gold standard AD (GS-AD) combined with a *prescription* topical anti-inflammatory therapy or antibiotic as recorded in the patient's chart.
   b) Clinically-significant (moderate) AD (**CS2-AD**): A gold standard AD (GS-AD) combined with a prescription topical anti-inflammatory therapy or antibiotic *or* an over-the-counter therapy was recommended and recorded in the patient's chart.
5. Lower cumulative incidence of **skin infections** as defined by**:**
   a) parent report using the following question on the twelve-month questionnaire:

Over the past 12 months, has a healthcare provider said your child has any type of skin infection?

b) chart review for provider diagnosis

c) chart review for medications (topical antibiotics)

6. Lower proportion with probable or predicted **asthma**:

a) As indicated by parent-reported provider diagnosis. Asthma will be considered present if the parent responds yes to this question:

Has your child ever been diagnosed with asthma by a healthcare provider?

b) The modified validated Asthma Predictive Index[9] in the intervention arm, which is a derived variable: To meet the definition, a child must meet one or more of the major criteria, which are:

- Parental history of asthma: At least one parent has a history of asthma *or* AD, from baseline questionnaire
- Inhalant allergen sensitivity, assessed from chart review

[Yes]: Has your child ever been diagnosed with hay fever or springtime allergies by a healthcare provider?

- Eczema, physician-diagnosed atopic dermatitis

and/or two or more of the minor criteria:

- wheezing without upper respiratory symptoms, which is assessed using questions from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire:

[Yes]: Has your child ever had wheezing or whistling in the chest in the past 12 months?

[4 or more]: How many attacks of wheezing or whistling has your child had in the past 12 months?

[Yes]: Has your child had wheezing or shortness of breath even when they do not have a cold?

- Allergic rhinitis, from chart review and this question:

[Yes]: Has your child ever been diagnosed with hay fever or springtime allergies by a healthcare provider?

- Peripheral eosinophilia (≥4%), from chart review

7. Lower prevalence of food allergy, measured as

a) the proportion with parental report of provider diagnosis, defined as a "yes" response to this question derived from the National Health Interview Survey[10]:

Has your child ever been diagnosed with a food allergy by a health care provider?

b) Parental report of a provider diagnosis of food allergy that was confirmed by prick testing or IgE blood test, defined as "yes" to both the previous question and this one:

Did your child have a positive test to any of the above foods using a skin prick test or blood test?

c) Parental report of immediate food allergy symptoms: a "yes" response to

Has your child ever had an allergic reaction within 2 hours of eating a food? (i.e. swelling of the face or lips, red rash, hives, stomach pain, vomiting, or wheezing/difficulty breathing)?

d) All three (3) of the above criteria, which may be described as near definite food allergy.

8. Lower prescription (Y/N) topical medication use or over-the-counter hydrocortisone usage in (1) all children and (2) those with AD only.

   a) Parent reported prescription topical medications, defined as either or both of the following responses to this question:

      Have you treated the red rash or eczema with any of the following? (check all that apply)

      Prescription steroid/cortisone cream/ointment from a healthcare provider (example, hydrocortisone 2.5% or triamcinolone cream or ointment)

      Prescription non-steroidal cream/ointment (example: Protopic, tacrolimus, Elidel, Eucrisa)

   b) Parent-reported prescription or over-the-counter topical medications, defined as the prescriptions above *or*:

      Hydrocortisone cream that you can buy without a prescription

      Other anti-itch cream that you can buy without a prescription

   c) Therapy(ies) recorded in chart; see definition for CS-2 above for description of prescription and over-the-counter therapies.

9. Lower severity of AD symptoms in intervention vs control *cases* as reflected by

   a) Lower mean Patient-Oriented Eczema Measure (POEM), a validated symptom index that includes sleep and itch[11]. Each of the questions has the possible responses of (0, No days | 1, 1-2 days | 2, 3-4 days | 3, 5-6 days | 4, Every day). To score, calculate the sum of the seven items for any respondent who answered at least five of the component questions (if the incomplete responses are <10% of the total responses).

      Over the last week, on how many days [nights, item 2] has your child's …

      … skin been itchy because of their eczema?

      … sleep been disturbed because of their eczema?

      … skin been bleeding because of their eczema?

      … skin been weeping or oozing clear fluid because of their eczema?

      … skin been cracked because of their eczema?

      … skin been flaking off because of their eczema?

      … skin felt dry or rough because of their eczema?

   b) Lower mean score on the 30-point Infants' Dermatitis Quality of Life Index (IDQOL) where higher scores indicate more impairment[12]. To score, sum the items below. A missing item will result in a missing response.

      Over the last week, HOW SEVERE do you think your child's dermatitis has been? In other words, how red, scaly, inflamed or widespread.
      4, Extremely Severe | 3, Severe | 2, Average | 1, Fairly Good | 0, No Eczema

      Over the last week, how much has your child been ITCHING AND SCRATCHING?
      3, All the time | 2, A lot | 1, A little | 0, None

Over the last week, what has your child's MOOD been?
3, Always crying, extremely difficult | 2, Very fretful | 1, Slightly fretful | 0, Happy

How many nights in the past week would you say your child's sleep was disturbed at night, not including routine feeding? 0-7

Over the last week approximately how much TIME on average has it taken TO GET your child OFF TO SLEEP each night?
3, More than 2 hours | 2, 1 to 2 hours | 1, 15 minutes to 1 hour | 0, 0 to 15 minutes

Over the last week, what was the TOTAL TIME that your child's SLEEP WAS DISTURBED on average each night?
3, 5 hours or more | 2, 3-4 hours | 1, 1-2 hours | 0, Less than 1 hour

Over the last week, has your child's eczema interfered with PLAYING OR SWIMMING?
3, Very much | 2, A lot | 1, A little | 0, Not at all

Over the last week, has your child's eczema interfered with them TAKING PART IN or ENJOYING OTHER FAMILY ACTIVITIES?
3, Very much | 2, A lot | 1, A little | 0, Not at all

Over the last week, have there been problems with your child at MEALTIMES because of the eczema?
3, Very much | 2, A lot | 1, A little | 0, Not at all

Over the last week, have there been problems with your child caused by the TREATMENT?
3, Very much | 2, A lot | 1, A little | 0, Not at all

Over the last week, has your child's eczema meant that DRESSING AND UNDRESSING the child has been UNCOMFORTABLE?
3, Very much | 2, A lot | 1, A little | 0, Not at all

Over the last week, how much has your child having eczema been a problem at BATH TIME?
3, Very much | 2, A lot | 1, A little | 0, Not at all

10. Delayed onset of AD, with age of onset determined by
    a) provider-recorded date of first diagnosis retrieved from record review of chart by research coordinator

       [Field:] Date (or age of child in months) of first AD diagnosis in the chart

    b) parental report of eczema age of onset to the nearest 3 months (based on quarterly contacts)

    Note: For interval-censored analysis, these variables will use the date of visit/response and previous visit/response as the end and start of the interval, respectively.
11. Lower mean days of disrupted sleep in the past week for infants reported by parents at 12 and 24 months, taken from the single item (#4) in the IDQoL.

5.2. Definitions for Subpopulation Analyses

In **exploratory analyses** we will investigate potential differences in treatment effect in subgroups with known or hypothesized risk or protective associations with AD using the approach given in section 5.5 below. The subgroups to be investigated are:

1. **Family history of atopy in a first-degree relative**, associated with approximately doubled risk of AD[13–16] and expected in 40 to 60 percent of the population, as found in our planning grant and suggested in other studies of IgE sensitization in the population[17]. This is one of

our stratification variables for randomization. If the elevated risk in this population is explained by filaggrin gene mutations affecting the skin barrier, then emollient use should be most protective in babies with a family history of atopy; this would point to recommending daily emollient use only in this high-risk population.

We will treat this as a binary variable (*yes* vs *no/don't know*) to the following question:

> Has at least one of your baby's blood-related PARENTS, BROTHERS OR SISTERS ever been diagnosed with asthma, eczema (atopic dermatitis) or hay fever (seasonal allergies)?

2. **Dry climate**, which we will measure using the average relative humidity over a year for the clinic's locality in records from the National Climate Data Center and Weather Service. More detailed methods will be developed, following the general approach in previous work, where a protective effect of RR 0.8 was observed in the highest humidity areas[18]. If emollient prevents AD by preserving the skin barrier, then the treatment effect should be greatest in low-humidity areas.
3. **Having pets or regular contact with farm animals at baseline.** Meta-analysis has found a protective effect for exposure to dogs (RR 0.72) and pets overall (RR 0.75), with more equivocal evidence for exposure to cats (RR 0.94)[19]. We expect about 30% of participants to own cats and 40% to own dogs based on large national pet ownership surveys. This analysis will be conducted in two steps. The first step will use a set of indicator variables for the following yes/no questions, and the second will use an overall binary variable for any regular contact with animals:

   > Does your baby have regular (at least weekly) contact with farm animals?
   >
   > Does your family own one or more dogs?
   >
   > Does your family own one or more cats?

   It is possible that farm animal contact will be collinear with other pets (babies with contact with farm animals may usually also have contact with both cats and dogs). In that case, the design variables may be coded as cats and dogs exclusive of farm animals.

   Because dogs, and pets in general, are protective, the treatment effect should be greater in families without pets, and/or with cats relative to dogs and other pets.
4. Treatment effect of **CeraVe** cream or ointment (at any time) vs all other emollients in the treatment arm vs controls. A study published since the start of this trial suggests that previously observed benefits from regular emollient use may be attributable to ceramides. Ceramides are present in both CeraVe cream and ointment, which is among the choices for study treatments. Although we are not powered to detect a significant difference from ceramide-containing emollients versus others, we plan to investigate whether use of these products is associated with a reduction in AD. The planned design variables for this analysis are for ceramides (1=CeraVe cream or ointment, 0=otherwise) and other emollients in the treatment arm (1=used, 0=not used). Controls will be used as the reference group.
5. The **baby's age at randomization** may moderate treatment effects, in that emollient use may be most protective if initiated early. Depending on the distribution of ages, this variable will be evaluated as age in days, or if needed, as a categorical variable for early vs late recruitment.
6. More **frequent bathing** may affect the skin barrier and change the treatment effect. Enhance because frequent bathers have more skin barrier damage. Reduce effect because emollient is not potent enough to overcome frequent bathing damage. Frequency of bathing is reported in days per week. This may be analysed as an ordinal variable or as a binary variable with the split determined by existing evidence.

7. **Caesarean birth** may affect the skin microbiome and modify the known effects of emollient on skin microbiome and barrier protection, though the direction of the effect is difficult to hypothesize.

In addition, **subgroup analyses by sex/gender and race and/or ethnicity** are required under the Inclusion of Women and Minorities policy of the NIH (NOT-OD-18-014). Coding for these variables will be as follows:

8. **Sex** of the baby will be coded as male/female; gender non-binary is not assessed. We have no a priori hypothesis about a differential treatment effect for biological sex.
9. **Race** will be coded using a set of design variables for the check-all-that-apply responses. African American race is associated with higher prevalence of atopic conditions, but lower prevalence of filaggrin defects. Thus, in spite of the elevated risk of eczema, we expect the treatment will likely be less effective for African American compared to other babies, because the mechanism of preserving the skin barrier would contribute less in this subpopulation. The source variable is coded as follows:

    What is your baby's race? (please check all that apply)
    American Indian or Alaska Native
    Asian
    Black or African American
    Native Hawaiian or other Pacific Islander
    White
    Other
    Prefer not to answer

10. **Hispanic ethnicity** will be treated as a binary variable, with "prefer not to answer" treated as missing, unless >10% of responses are missing, in which case ethnicity will be coded with two design variables, (1=Hispanic/0=not, 1=missing/0=present) based on the following question:

    What is your baby's ethnic group?
    Hispanic or Latino
    Not Hispanic or Latino
    Prefer not to answer

5.3. Analysis of Primary Endpoint

For the primary analysis, we contrast the risk of diagnosed atopic dermatitis (AD) by two years of age for the intervention versus control groups under an intention-to-treat (ITT) assumption, analyzing all subjects according to the group to which they were allocated regardless of adherence or group crossover, and imputing missing outcome values using multiple imputation methods. The measure of interest is the ratio of the intervention:control proportions, a relative risk (RR) measure. If emollient use prevents AD, the RR will be significantly smaller than 1.

Estimation of the relative risk will be by log-binomial regression using a generalized linear model with a log link and binomial distribution. A binary indicator variable will represent assigned **study arm** (intervention=1, control=0). The exponentiated coefficient of this variable, $\exp(\beta_1)$, estimates RR. We will test $\beta_1 \neq 0$ at the 0.05 level of significance. If $p<0.05$, we will consider RR significantly different from 1, meaning that there is strong evidence for the effect of emollient use on AD in very young children.

Stratification variables will also be included in the model to avoid bias in estimates of effects and standard errors. The stratification variables are **family history of atopy in a first-degree relative** and **recruiting clinic**, which will be included as a **random effect**. Because there are 45 recruiting

clinics in the study, clinic cannot be modelled as a fixed effect without losing statistical efficiency. No other baseline characteristics will be included.

Equation 1

$$log(p[AD_{ij}]) = \beta_0 + \beta_1 Arm_{ij} + \beta_2 FamHx_{ij} + b_j$$

In this model, the variable *Arm* represents assigned **study arm** (intervention=1, control=0) for participant i recruited from clinic j. The variable *FamHx* represents family history of atopy in a first-degree relative (1/0). The term b_j is a random intercept for the primary care clinics where participants were recruited. The exponentiated intercept coefficient (exp(β_0)) represents the cumulative prevalence of AD in the control arm, while exp(β_1) estimates RR.

Alternative strategies could be used to overcome convergence issues. If this model fails to converge, alternatives include substituting a Poisson model with robust variance estimates, providing starting values for estimation in the statistical software, or using an alternative algorithm.

Missingness in the primary outcome is addressed in detail the "Missing Data" section below. Consistent with the ITT assumption, if <5% of participants are missing the outcome variable, we will analyse this outcome under **multiple imputation** or using **Bayesian** methods as the primary approach.

In *reporting findings*, we will present the RR estimate with 95% confidence interval; if the outcome is imputed, both this and the complete case finding will be reported. We will also report the treatment effect as the absolute (rather than relative) risk difference. This can be calculated as the difference in the adjusted group prevalence using average conditional predicted risk. Standard errors (SE) and 95% confidence intervals can be obtained by the delta method, which is a standard method to compute SE of nonlinear transformations and can be executed using Stata's -margins- command, for example. The primary analysis will be repeated using raw (not model-based) estimates of risk and relative risk, to check for the influence of software defaults or model flaws on the findings.

5.4. Analysis of the Secondary Endpoints

Definitions of secondary endpoints are in section 5.1

The following **binary outcomes** will be evaluated with log-binomial models similar to Equation 1 for the primary outcome. When comparing intervention versus controls, we will use a Wald test for the intervention regression coefficient at the 0.05 level of significance.

2. As secondary/sensitivity analyses, we will test the intervention effect with alternative definitions of AD at 24 months, namely:
    a) Complete case analysis of the primary endpoint (GS-AD), provider diagnosis, adjusting for stratification variables as well as covariates that we find to be associated with missing AD status;
    b) PR-AD- Parent report of a provider diagnosis at any point in the ITT dataset;
    c) UK Working Party in the ITT dataset;
    d) CEQ-AD- Children's Eczema Questionnaire (CEQ) in the ITT dataset;

3. Cumulative incidence of AD at 18 months.

In addition to the binary models, we will conduct a multivariate or latent variable analysis to estimate cumulative incidence in each treatment arm using multiple candidate definitions and estimating the correlations between the definitions.

4. Cumulative incidence of AD treated with prescription and/or over-the-counter medication(s)
    a) Clinically-significant severe AD (CS1-AD)
    b) Clinically-significant moderate to severe AD (CS2-AD)

Non-AD (but still binary) outcomes include the following:

5. Probable or predicted asthma by the modified Asthma Predictive Index, and/or symptoms of asthma such as wheezing or prescribed bronchodilator.
6. Food allergy, defined by:
    a) Parental report of provider diagnosis of food allergy
    b) Positive prick testing or IgE blood test
    c) Parental report of immediate food allergy symptoms
    d) Near definite FA- provider diagnosis, positive test, and immediate symptoms
7. Prescription topical medication use or over-the-counter hydrocortisone use in (1) the ITT dataset, and (2) the AD dataset
    a) reported by parent
    b) identified during chart review

For **continuous** outcomes, use histograms and normal quantile plots to check for obvious lack of symmetry. Test for group differences with a linear regression model similar to the log-binomial models described above, using bootstrapped standard errors if the distribution of responses is non-normal.

8. In the AD dataset, severity of symptoms as measured by:
    a) Mean Patient-Oriented Eczema Measure (POEM) (a) averaged and (b) summed across all items in the ITT dataset.
    b) Mean score on the 30-point Infants' Dermatitis Quality of Life Index (IDQOL) summed across items in the ITT dataset

Age at onset will be tested using either pooled logistic regression or time-to-event methods for interval-censored data. For these analyses, age of onset will be indexed to the quarterly contact when the parent reported a diagnosis or to the closest corresponding age if the first diagnosis date is in the child's medical chart. Although we may not have sufficient sample size to detect an age-dependent treatment effect, it is possible that the greatest protective effects will be observed at early ages. Kaplan-Meier curves or similar visualizations may help to evaluate differences in treatment effect by age of onset.

9. Age of onset to the nearest 3 months determined by
    a) parental report of eczema from quarterly contacts or annual questionnaires
    b) provider-recorded date of first diagnosis retrieved from record review of chart by research coordinator indexed to the nearest quarter of follow-up

Mean days of disrupted sleep will be treated as a **count** variable and tested with a Poisson model similar to those described above.

10. Lower mean days of disrupted sleep in the past week for infants reported by parents at
    a) 12 months
    b) 24 months

5.5. Exploratory Subgroup Analyses

In exploratory analyses we will investigate potential differences in treatment effect in subgroups with known or hypothesized risk or protective associations with AD. These are defined in the "Definitions for Subpopulation Analyses" section above.

For each analysis, we will estimate differences in the treatment effect on both the absolute (i.e. risk difference) and relative (i.e. ratio) scales. After calculating the raw differences, we will estimate them based on a model that incorporates the same variables as in other analyses, but with main effects and interactions for the subgroup variables outlined above. Most of these are either binary or continuous; in the case of a multi-level categorical variable, we will use a set of design variables. The analysis addressing ceramides will only use main effects, without interaction terms. The model will use the full ITT dataset with provider-diagnosed AD as the outcome. The p value for the single interaction coefficient (or for the combination of interaction coefficients, if multiple design variables are used) will provide an estimate of statistical significance for a difference in treatment effects in the subgroups being modelled. We plan to use a significance threshold of 0.10 for identifying effects that may warrant further investigation. (Designing the trial for a lower threshold was not feasible.)

More important than p values, we plan to rely on the magnitude of effects to determine whether the intervention is more effective in some subgroups than others. It is difficult to specify a threshold for the magnitude of difference in advance. The planned presentation of results is given in Table 5.

5.6. NIH-required Subgroup Analyses

Subgroup analyses by baby's sex, race, and ethnicity will be conducted similarly to the subgroup analyses above, using the full ITT dataset with provider-diagnosed AD as the outcome (which is the study's primary outcome). A regression model with main effects and interactions with intervention assignment and other study design variables will be used to generate estimates.

We will report the numbers of participants with and without AD by 12/24 months in the intervention and usual care arms in each subgroup; the treatment effect (RR) using the group with the lowest-risk group as the reference category; interaction effects with 95% confidence intervals. Some groups defined by race may be very small for statistical inference. In follow-up analyses, we will investigate the possibility that differences in treatment effects, if any, are confounded by other factors, e.g. climate or frequency of emollient use, if these are found to be associated with the primary outcome.

5.7. Analysis of Effect of Reported Emollient Use

Because the intervention uses an accessible, non-prescription topical emollient, either study arm might have users and non-users (compliant/non-compliant with study assignment). In the spirit of a *per-protocol analysis,* similar to the main analysis, we will classify participants by their reported emollient use (>weekly, on average, for the time up to diagnosis or end of follow-up) rather than assigned intervention arm. Under this coding, some participants assigned to the treatment arm might be non-users, and others assigned to the control arm may report regular emollient use; those individuals would be in different groups than under the main analysis, which uses assigned treatment arm.

Parent-reported frequency of emollient use (in days per week) will be summarized for the intervention and control arms for each quarterly follow-up time point from age 3 to 24 months (8 quarters). In this analysis, we will exclude observations after a diagnosis of AD, because emollient use is likely to reflect treatment rather than prevention. For example, if a parent reports a diagnosis of AD on the 9-month contact, that child's emollient use at 3 and 6 months will be included, but not 9 months or later. All of the definitions of AD diagnosis will be considered, i.e. GS-AD, PR-AD, CEQ-AD, etc. For missing responses, we will carry the last observation forward. Distributions over time will be graphed.

The relationship between frequency of emollient use and AD will be tested using a variable that is the average of each individual's frequency responses. We hypothesize that the intervention will increase the frequency of emollient use, and that more frequent emollient use will be associated with lower incidence of AD. If this is true, we expect that frequency will be associated with study arm (using a two-sample t-test or Wilcoxon rank-sum test, if skewed), that study arm will be associated with prevalence of AD (primary analysis), that higher frequency of emollient use will be associated with lower prevalence of AD (Equation 1 with emollient frequency substituted for study arm), and that including both treatment arm and emollient frequency in a model with AD as the outcome will change the estimate of treatment effect, which will be taken as evidence that frequency of emollient use is in the causal pathway.

5.8. Evaluation of Success of Blinding

Because of the nature of the intervention, our ability to maintain blinding for most participants and study personnel is limited. However, the success of blinding is particularly relevant in the chart reviews that we plan for evaluating the primary outcome. We plan to use Bang's Blinding Index (BI)[20] in the context of chart reviews by including a single question on the chart abstraction form asking research coordinators to indicate whether they

1. Strongly believe this participant is in the intervention arm
2. Somewhat believe this participant is in the intervention arm
3. Somewhat believe this participant is in the control arm
4. Strongly believe this participant is in the control arm
5. Don't know

Counts of responses will be compiled in a 2x5 matrix and the BI computed using statistical software, e.g. the -blinding- module in Stata. The index ranges from -1 to 1, where 1 indicates complete lack of blinding, 0 perfect blinding, and -1 perfect opposite guessing. It can be used to detect a low degree of blinding, response bias and different behaviors in two arms. We plan to compute this index stratified by research assistant and overall, using point estimates and confidence intervals.

5.9. Missing Data

The approach to missing data will be guided by sources such as Jakobsen et al[21] on missing data in randomized trials.

Definition of missingness in the primary outcome: The primary outcome, AD by 24 months of age, will be ascertained through review of medical records by research personnel blinded to intervention status and will be considered *not* missing if either (1) a diagnosis of AD is found for any visit before age 24 months (±3 months), *or* (2) no diagnosis is found *and* the child had at least one visit in the 24-month window. The outcome will be considered missing if those conditions are not met, i.e. we

find no diagnosed AD before age 2 years *and* no clinic visit within ±3 months of the child's second birthday.

COVID-19 pandemic as a cause of missingness: Because the primary outcome depends on an in-person clinic visit, it is likely to be missing for children who would otherwise have had visits during periods when the clinic was not offering in-person care or when parents declined to bring children for non-urgent care. The study team discussed extending the window for chart reviews to mitigate this effect, but this would require contacting parents for consent and was not adopted.

Missingness in other variables: Other variables from parent report will be considered missing if the response is absent or "don't know/unsure" or similar. In chart reviews, missingness will occur if a visit is not found, but if a visit is found, a "not found" for a particular category (e.g. medication) will be considered a non-missing "no." Validated multi-item scales will be scored according to published guidelines when available. When guidelines are not available, decisions about how to treat missing responses will be made and recorded before the dataset is locked for analysis.

If ≤5% of observations are missing the primary outcome, then multiple imputation methods will not be of benefit and we will perform analysis without imputation. The treatment assignment, family history of atopic dermatitis, and recruiting clinic are assigned or used to create arm assignments and so will be complete for all participants.

If >5% of observations are missing outcomes, then further steps are needed. In addition to the analytic steps described here, we will discuss with members of the study team who interact with participants and clinic staff and may have insight into reasons for loss to follow-up that may or may not be reflected in recorded data. As a first step, we will create an indicator variable R=1 if the outcome is missing, R=0 if not missing. This variable R can be used to test whether missingness is associated with other variables, particularly:

- Study arm
- Family history of atopy
- Date of enrollment in study
- Parent report of AD
- Child's Eczema Questionnaire (CEQ) signs of AD
- UK Working Party criteria for AD
- PBRN

If differences are found (at $p<0.10$, approximately, for an inclusive approach) then covariate-dependent missingness at least partly explains the missingness mechanism. Any such variable should be used in the multiple imputation model (or included in the main model without imputation) to produce unbiased estimates.

Multiple imputation will be performed using iterative chained equations over five (5) imputation sets. At the time of writing, the performance of multiple imputation when the model includes a random effect, such as the recruiting clinic in our model, is not well understood, and software to run the model we have proposed under multiple imputation is not readily available. (The estimation command is not available in Stata version 16, for example). Alternatives include (a) substituting a Poisson or logistic model, (b) omitting clinic, which should not be strongly associated with treatment outcome, or (c) Bayesian approaches, which could be especially useful if we suspect that data are missing not at random. The multiple imputation results will be considered the primary findings and will be reported along with complete case analysis.

5.10. Sensitivity Analyses

The sensitivity of findings to the choice of model and missingness assumptions will be addressed by some of the analyses already described, e.g. using different definitions for diagnosed AD in

secondary analyses, and conducting both complete case and imputed analysis. In addition, we plan to conduct "worst case" and "best case" analyses, and to calculate how many of the missing outcomes in the intervention arm would need to have AD in order for the point estimate of treatment effect to be null (RR=1).

The COVID-19 pandemic may affect the discovery of the primary outcome due to fewer office visits. We will examine potential changes over time in (a) missing primary outcome, i.e. no diagnosed AD and no primary care visit within the window of time for the 24-month assessment, and (b) the prevalence of the primary outcome in non-missing data.

Evidence also suggests that the incidence of respiratory syncytial virus (RSV) decreased during the pandemic, which may affect secondary outcomes related to wheezing. We will conduct a similar sensitivity analysis for a change in prevalence in RSV in the study population over time.

Additional sensitivity analyses may be identified as the datasets are prepared for analysis and before the breaking of the blind. Some accounting of the amount of emollient requested, for example, may be useful.

5.11. Safety Analyses

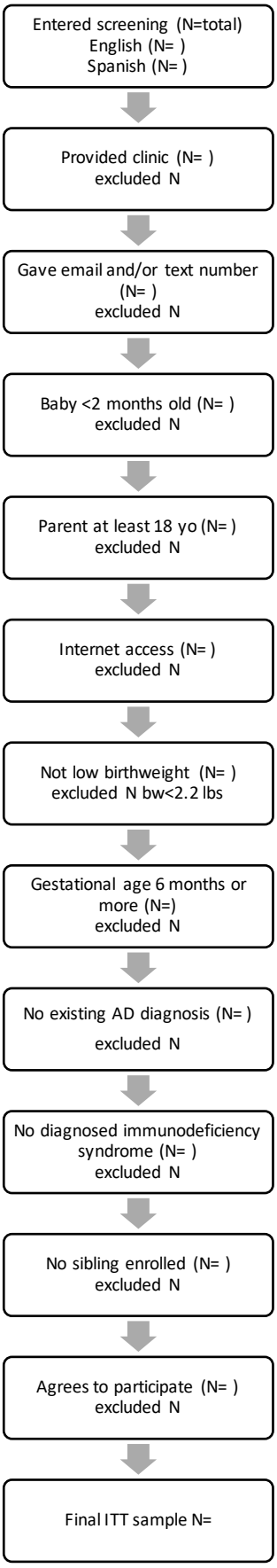
The proposed intervention, use of a lipid-rich emollient, poses very little risk. For this reason, we defer to the DSMB to review safety information and recommend follow-up analysis. A priori safety analyses are specified elsewhere and included here for reference, but are not planned as part of the primary analysis.

The most plausible adverse events (AEs) are skin reactions to added ingredients in the study emollients, though we have intentionally selected simple formulations. Participants are asked to report any skin care product-related adverse event during quarterly contacts or communications with the clinical coordinating center. Research coordinators will record any skin care product-related AEs reported in the chart. We will provide the DSMB with annotated summaries of adverse events categorized by type and specific emollient, along with the denominator of dyads who selected the specific emollient. A dyad may be counted more than once if they select different emollients at different time points. Adverse reactions that affect >5% of dyads randomized to either arm will be reported.

Participants are asked to report any serious adverse events (SAEs) during quarterly contacts. The SAE most appropriate in this population include inpatient hospitalization or prolongation of hospitalization and a significant medical incident. AEs and SAEs are assessed to identify unanticipated problems. Unanticipated problems are unexpected, related to participation in the research, and places participants at a greater risk of harm than was previously known. We also record any deaths.

5.12. Figures and tables

Figure 1: Screening flowchart (separate from CONSORT diagram, Figure 2)



Future questions related to CONSORT figure:

How to include withdrawn from certain activities? (partial withdrawal) Often reach out shortly after randomization b/c unable to fully comply but may be willing to complete questionnaires.

Also variable in how much emollient requested

Figure 2: CONSORT Flow Diagram

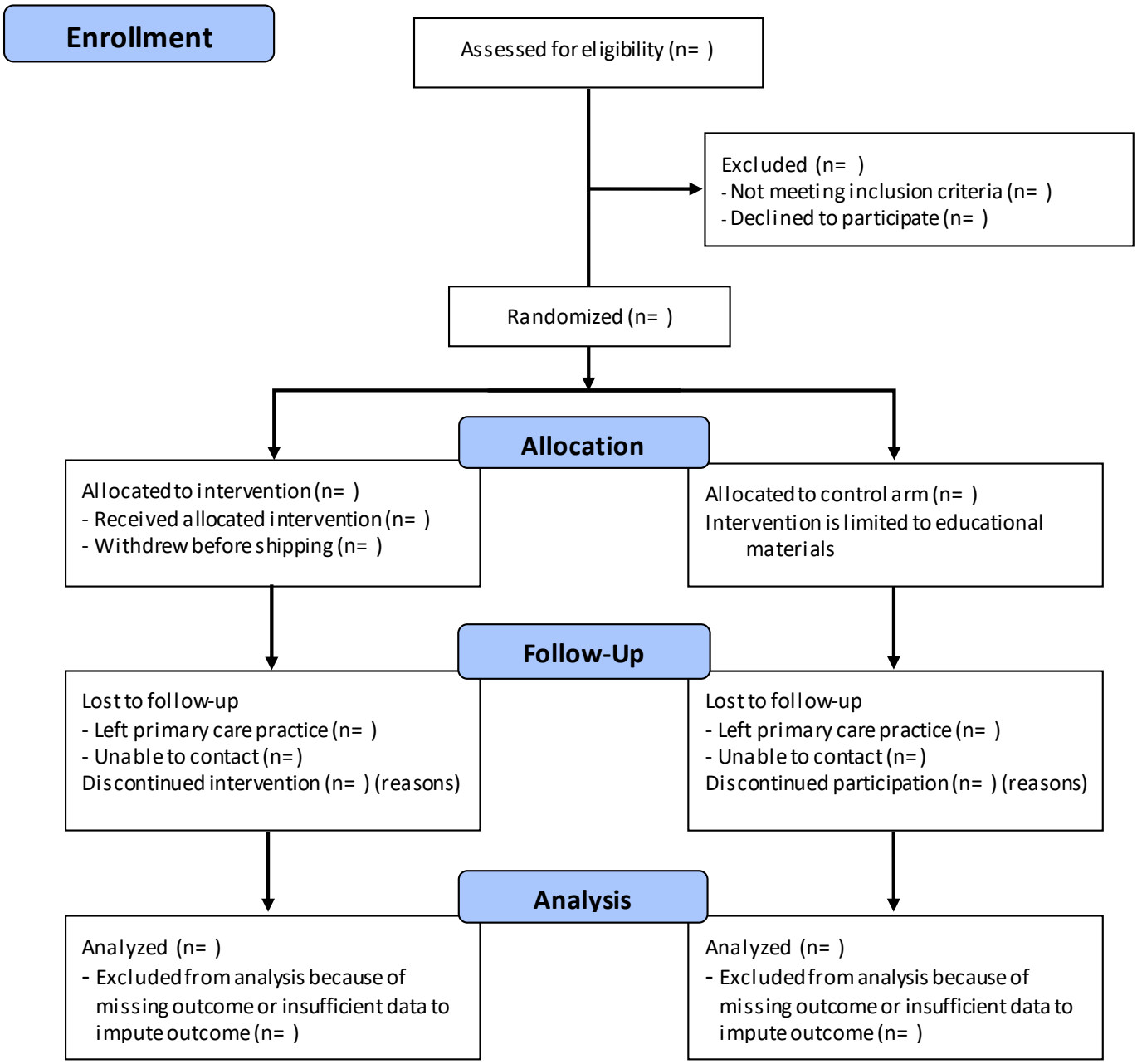


Figure 3: Follow-up in the randomized/intention-to-treat (ITT) population

Time points 1, 5, 9 (gold): Long-form questionnaires; time points 2, 3, 4 and 6, 7, 8 (white): Brief follow-up.

m: months; n: count; %: percent of randomized total in arm; D/C: discontinued, confirmed by study personnel; moved: moved out of area; lost: lost to follow-up without being able to confirm a reason; na: not applicable.

Responded: full or partial response given; Missed: no response at given time point but later response exists; Withdrawn: No response at this or later time contacts (chart review may be complete). The sum of each row should equal the sum of (responded + missed) in the previous row.

Table 4: Planned summaries of study variables

Table Title	Population	Time Point(s)	Endpoint	Endpoint Type	Summary Statistics by Treatment Assignment
Disposition	ITT	Baseline to 24m each 3m	Disposition	Categorical (AD, no AD, lost to follow-up)	Count
Baseline Variables	ITT	Baseline	Age at enrollment	Weeks	n, mean, SD, Median, min, max
			Parental atopy	Binary (Y/N)	p% (x/n)
			Siblings with atopy	Binary (Y/N)	p% (x/n)
			Any parent or sibling with any atopy	Binary (Y/N)	p% (x/n)
			Home location	Categorical (urban, suburban, rural, etc.)	p% (x/n)
			Farm living	Binary (Y/N)	p% (x/n)
			Dog ownership	Binary (Y/N)	p% (x/n)
			Cat ownership	Binary (Y/N)	p% (x/n)
			Probiotic pills	Binary (Y/N)	p% (x/n)
			Dry skin	Binary (Y/N)	p% (x/n)
			Baths/week	Count (0-7+)	p% (x/n) n, mean, SD, Median, min, max
			Prior emollient use	Binary (Y/N)	p% (x/n)
			Prior emollient type	Categorical	p% (x/n)
			Prior emollient brand	Descriptive	p% (x/n)
			Prior emollient use per week	Count (0-7+)	p% (x/n) n, mean, SD, Median, min, max
			Gender	Binary (M/F)	p% (x/n)
			Ethnicity	Binary (Hispanic)	p% (x/n)
			Race	Categorical	p% (x/n)
			Education level	Categorical	p% (x/n)
Emollient Choices	Treatment Group	Baseline	Emollient choice-baseline	Categorical	p% (x/n)
		24m or last refill	Emollient choice-end of study	Categorical	p% (x/n)
			Switched from baseline	Binary (Y/N)	p% (x/n)

Table Title	Population	Time Point(s)	Endpoint	Endpoint Type	Summary Statistics by Treatment Assignment
Cumulative incidence of AD	ITT	24m	Primary outcome: Provider diagnosis of AD in patient chart	Binary (Y/N)	Relative risk (RR) for cumulative incidence
	ITT	12m,24m	Provider diagnosis of AD in patient chart at age 1 year and age 2 years	Binary (Y/N)	RR
	Complete case	12m,24m	Provider diagnosis of AD in patient chart (complete case)	Binary (Y/N)	RR
	ITT	12m,24m	Cumulative incidence of AD by parental report of provider diagnosis	Binary (Y/N)	RR
	ITT	12m,24m	Cumulative incidence of AD by parental report of Children's Eczema Questionnaire	Binary (Y/N)	RR
Age of onset of AD	ITT	All time points	Age of onset by chart review, parent report	Time to event	Kaplan-Meier
Skin Problems	ITT	12m,24m	Dry Skin	Binary (Y/N)	p% (x/n)
			Diagnosed eczema	Binary (Y/N)	p% (x/n)
			Red rash	Binary (Y/N)	p% (x/n)
			Itching	Binary (Y/N)	p% (x/n)
			Areas of rash	Categorical	p% (x/n)
Skin infections	ITT	12m,24m	Presence/absence at any time	Binary (Y/N)	p% (x/n)
			Type	Categorical	p% (x/n)
Rash treatment	AD population	12m,24m	Rash treatment Y/N	Binary (Y/N)	p% (x/n)
			Prescription treatment Y/N	Binary (Y/N)	p% (x/n)
			OTC treatment Y/N	Binary (Y/N)	p% (x/n)
			Specific type	Categorical	p% (x/n)
Skin care	ITT	12m,24m	Baths/week	Count (0-7)	p% (x/n) n, mean, SD, Median, min, max
		12m,24m	>2 baths/week	Binary (Y/N)	p% (x/n)
		12m,24m	>1 bath/week	Binary (Y/N)	p% (x/n)
		All time points before AD diagnosis, if applicable	Frequent emollient user: Report 3 or more days per week at majority of follow-up points	Binary (Y/N)	p% (x/n)
		Q3 months	Moisturizer use Y/N	Binary (Y/N)	p% (x/n)
			Emollient use days/week	Count (0-7)	n, mean, SD, Median, min, max
			Emollient type	Categorical	p% (x/n)
			Which emollients	Categorical	p% (x/n)

Table Title	Population	Time Point(s)	Endpoint	Endpoint Type	Summary Statistics by Treatment Assignment
Breathing Problems	ITT	12m,24m	Ever wheeze	Binary (Y/N)	p% (x/n)
			Number of wheeze events over past year (cat)	Count	p% (x/n)
			Wheeze without cold	Binary (Y/N)	p% (x/n)
			Diagnosed asthma	Binary (Y/N)	p% (x/n)
			Asthma predictive index-Y/N (derived)	Binary (Y/N)	p% (x/n)
Allergies	ITT	12m,24m	Skin Prick Test or Blood test	Binary (Y/N)	p% (x/n)
			Food allergy symptoms	Binary (Y/N)	p% (x/n)
			Food exposure	Binary (Y/N)	p% (x/n)
Severity of symptoms and influence on quality of life	AD population	12m,24m	POEM score (0-28)	Continuous	n, mean, SD, Median, min, max
			IDQOL score (0-30)	Continuous	n, mean, SD, Median, min, max
	ITT	12m,24m	Parent-rated health status	Ordinal (1-5)	p% (x/n) n, mean, SD, Median, min, max
			Days of disrupted sleep in the past week	Count (0-7)	p% (x/n) n, mean, SD, Median, min, max
Adverse events	ITT	12m,24m	Adverse reaction to skin product	Binary (Y/N)	p% (x/n)
			Type	Categorical	p% (x/n)
			Ended	Binary (Y/N)	p% (x/n)
			Severity	Categorical	p% (x/n)
			Require HCP visit	Binary (Y/N)	p% (x/n)
			Diagnosis	Categorical	p% (x/n)
			AE Treatment-Y/N	Binary (Y/N)	p% (x/n)
			AE Treatment-name	Categorical	p% (x/n)
			SAE listing	Narrative	n/a
Contact info change	ITT	Any time			p% (x/n)

Table 5. Exploratory analyses

Subgroup	Intervention cumulative incidence	Usual care cumulative incidence	Difference (risk difference) 90% CI	Difference in differences	Risk Ratio 90% CI	Difference (ratio scale)	P value for interaction
Family history of atopy Yes No							
Climate Dry Wet							
Domestic animals Any None Cat(s) Dog(s) Farm animal(s)							
Sex Female Male							
Age at randomization Youngest Middle Oldest							
Emollient type used CeraVe Others None							

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