## STATISTICAL ANALYSIS PLAN for the PreventADALL Randomised Clinical Trial

### Administrative information:

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<tbody>
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<td>Kirkeveien 166, 0424 Oslo, Norway</td>
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<tr>
<td>EudraCT number / REC no</td>
<td>Ethics committee number: 2014/518 PreventADALL (Norway and 2014/2242-31/4 Sweden)</td>
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<tr>
<td>Trial title</td>
<td>PreventADALL (Preventing Atopic Dermatitis and ALLergy in children)</td>
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<td>Trial ID</td>
<td>PreventADALL</td>
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<td>Trial registration number</td>
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<tr>
<th>SAP version and date:</th>
<th>This SAP is version 1.0, dated May 3rd 2019</th>
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<tr>
<td>Protocol version</td>
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Valid from October 2018

Oslo University Hospital
STATISTICAL ANALYSIS PLAN for the PreventADALL Randomised Clinical Trial

SIGNATURE PAGE

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03/05/2019

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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report forms</td>
</tr>
<tr>
<td>FA</td>
<td>Food allergy</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>OFC</td>
<td>Oral Food Challenge</td>
</tr>
<tr>
<td>PPS</td>
<td>Per Protocol Analysis Set</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SPT</td>
<td>Skin prick test</td>
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1 Introduction

1.1 Background and rationale
Atopic diseases often start in infancy with atopic dermatitis (AD), and food allergy, followed by asthma and subsequently allergic rhinitis (the “atopic march”). The mechanisms of development of allergic sensitisation (AS), reflecting an unwanted break of tolerance to harmless environmental proteins are unclear. On a background of genetic and epi-genetic variation, a dysfunctional barrier (skin/airways) combined with exposure to/composition of the body’s microbiota are probably directly involved in early atopic development, and AD appears to precede allergic sensitisation. Reduced skin barrier, found with protein defects associated with filaggrin mutations, are also associated with AD and asthma, but explain only some cases of disease. Airway epithelial barrier defect, including both upper and lower airways, also associated with filaggrin mutations suggest a common inflammatory asthma pathway. However, it was recently found that patients with mutations in the FATP4 gene, encoding a fatty acid transporter protein expressed in skin have increased incidence of allergies, suggesting that skin lipid metabolism is directly involved in allergy development. Skin care (lipid moisturizers /emollients) is important in treating established atopic eczema.

Theoretically, primary prevention of atopic disease should be possible through improving the barrier function. This has not yet been tested in general cohorts, but two pilot studies and two studies in high-risk infants suggest that regular use of oil-baths or use of emollients in early infancy may reduce xerosis (dry skin) (prior to atopic eczema) or AD at approximately 6 months of age. Regular use of bath-oil significantly reduced the xerosis and indicated reduced development of later atopic eczema, while a pilot study from the UK suggested that among 22 neonates subjected emollient skin care from birth, 15% had atopic eczema by 1.5 years, which was lower than their historic controls. Further, during establishment of the PreventADALL (in 2014), two studies including around 100 and 430 high-risk infants reported a relative risk reduction of developing AD of 30-50% by daily use of emollients up to six months.

Infants may have several sources of allergen exposure: orally through the diet, inhalation of allergens (e.g. aerosolised when cooking, inhalation of indoor dust) and trans-dermally through damaged skin. A sub-optimal microbiotic environment in the gastrointestinal tract and transdermal allergen exposure may modulate the immune system and prevent tolerance development. However, oral allergen exposure is important for the induction of tolerance development. Supplementary breast-feeding during early allergen introduction may thus boost immunomodulation and tolerance development. This questions the present Norwegian guidelines advocating exclusive breastfeeding for six months and delayed introduction of solid foods including fish, milk, egg, nuts and peas in “risk” patients, also since studies suggest that early, rather than later introduction of food allergens may reduce allergic sensitization. The mechanisms, timing and amount of allergen exposure needed for natural allergen tolerance development is not clear.

1.2 Trial Objectives

1.2.1 Primary Objective
STATISTICAL ANALYSIS PLAN for the PreventADALL Randomised Clinical Trial

The primary object is to test if skin care (oil bath and facial cream) from 2 weeks of age and early food intervention starting between 3-4 months of age can prevent atopic dermatitis and food allergy.

1.2.2 Secondary Objectives

The secondary objectives of this study are: to determine if skin care (oil bath and facial cream) from 2 weeks of age and early food intervention starting between 3-4 months of age can prevent

- Allergic sensitization (SPT and specific IgE)
- Asthma (recurrent bronchial obstruction)
- Allergic rhinitis

1.2.3 Exploratory Objectives (if applicable)

The PreventADALL consists of two parts; one RCT as described in this SAP, as well as an exploratory study, assessing factors early in life that may impact development of non-communicable diseases (NCDs). The exploratory part of PreventADALL involves a broad array of exploratory approaches, and will not be detailed further in the SAP.

2 Trial Methods

2.1 Trial Design

PreventADALL is a two-country, superiority 2x2 factorial randomized controlled intervention trial of two interventions: skin care from 2 weeks to months of age and early food introduction by 3-4 months, and two main outcomes (atopic dermatitis at 12 months and food allergy at 36 months). Intervention allocation is a 1:1:1:1 ratio (no intervention vs skin care 0-9 months + early food introduction by 3-4 months alone vs early food introduction by 3-4 months alone). The investigators assessing the outcomes are blinded to the randomisation, as is the study statistician.

For ethical reasons it was decided to assess the primary outcome of skin interventions for Atopic Dermatitis as soon as possible, which was at 12 months of age. Due to the changing pattern of food allergy in the first years of life, and to align with other food allergy primary prevention studies, it was further decided that the main outcome of the food intervention (food allergy to interventional allergens) would be assessed at 36 months. It is therefore expected that some adjustment will be determined prior to the assessment of the food allergy outcome assessments, including the full factorial design. Amendments to the planned analyses of 36-month outcomes will be duly recorded and a new version of the Statistical Analysis Plan will be closed and signed prior to locking the final database, in good faith working with the database ignoring the randomisation allocation.
2.2 Randomisation
Eligible children are allocated at birth in a 1:1:1:1 ratio between the four intervention groups (no intervention vs skin care 0-9 months + early food introduction by 3-4 months vs skin care 0-9 months alone vs early food introduction by 3-4 months alone).

To reduce the risk of contamination of interventions within any “bærelgruppe” (Maternity group), we performed a computerized stepped wedge randomization procedure based upon area of living and time of birth. The procedure was as follows: all subjects born in the same yearly quarter AND belonging to the same postal code or “bydel” were allocated the same treatment. The list of postal codes and bydel used in this randomization procedure is provided in Appendix 1 and the quarters were defined as January 1-March 31; April 1-June 30; July 1-September 30; October 1-December 31 in Norway and June 4-Sept 3; Sept 4-Dec 3; Dec 4-March 3; March 4-June 3 in Sweden. This shift in quarters relates to the later inclusion start date in Sweden.

The randomisation process above is more detailed than what is described in the Protocol. Details of the randomisation including the final random allocation list is unavailable to unauthorized trial personnel.

2.3 Sample size
Sample size calculation was based on the primary endpoint atopic dermatitis at 12 months and not based on the primary endpoint of allergy at 36 months, mainly due to the lack of available data for the latter at the time of start of study (2014). The calculation is based upon the prevalence (ECA study) of AD at two years of age (23.2%) for skin care intervention only. No sample size calculation was performed for the early food introduction intervention due to lack of available data.

The sample size calculation in PreventADALL assumes a 30% reduction of AD (i.e. 23.2% vs 16.24%) with the skin care intervention and assumes no interaction with the second intervention of early food introduction. To obtain 80% power with alpha=0.05 and two-sided testing, the Protocol states that 2400 babies would be sufficient. The recruitment target was set at 2700 pregnancies to allow for 12.5% drop-out rate. No upward adjustments in the sample size have been made for the expected cluster effect induced by the stepped wedge randomization procedure.

There is however an error in the power calculation in the Protocol. Given the assumptions above, only 511 babies (576 babies after accounting for drop-outs) are needed per group at the margins (1022 babies total; 1152 after accounting for drop-outs). The error is most likely that the per group number was multiplied by 4 (for each of the 4 groups in the 2x2 factorial design) instead of 2 (for each of the 2 groups at the margins based on the skin care intervention). The study in fact has >99% power to detect a 30% reduction of AD from 23.2% to 16.24%.

The calculations above assume no multiple testing correction for the two primary outcomes (AD at 12 month and allergy at 36 months).
STATISTICAL ANALYSIS PLAN for the PreventADALL Randomised Clinical Trial

The rationale for assessing food allergy first at 36 months of age is due to recent reports, published after the PreventADALL study was well in progress, that led to a reassessment of the appropriateness of time of the first report of the main outcomes. The LEAP\textsuperscript{13} and EAT\textsuperscript{14} studies, both assessing introduction of allergenic foods from infancy in high risk and general population recruited babies, respectively were published in the NEJM in 2015 and 2016. Both studies assessed food allergy at 36 months of age, partly because natural tolerance development is likely in some children up to this age. The PreventADALL is important and unique in terms of food introduction as well as skin care in infancy in a large mother-child general cohort, and we therefore believe that assessing food allergy at the same time as these two pivotal studies will improve likelihood of solid evidence as to the effectiveness of preventing food allergy by three years of age, albeit with different strategies.

Likewise; the main outcome of Atopic dermatitis (AD) will be assessed first at 12 months of age.

*Rationale:* Two clinical trials of daily emollients from shortly after birth, assessed their main outcomes in high risk babies first at 6 months or 32 weeks of age, in line with end of their intervention\textsuperscript{15,16}. With the PreventADALL study being the first large study in a general population birth cohort, we deemed it important to report on the first main outcome endpoint after the intervention has stopped (9 months) as soon as possible. The infants are investigated at 12 months of age, with detailed skin examination. Although for the factorially designed interventions, both outcomes should ideally be assessed at the same time, we find it ethically challenging to delay outcome assessment for two years, in case of significant improvement of the intervention. It is unlikely that reporting the effect of the primary prevention use of specifically produced bath oil in infancy will affect behavior of the mothers of 2-3-year-old children in terms of skin care, in a way that interferes with the assessment at 3 years of age. Also, we have detailed blinded assessments of skin disease at 6-12-24-and 36 months of age to adjust for potential behavior modification.

Therefore, for these ethical and clinical reasons, we do not find it reasonable to adjust the level of significance for multiple testing across the 12 months AD and 36 months FA (food allergy) outcomes.

### 2.4 Statistical Framework

#### 2.4.1 Hypotheses Tests

<table>
<thead>
<tr>
<th>Biological hypothesis</th>
<th>Null hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superiority of the skin care intervention compared to no intervention as primary prevention of atopic dermatitis at 12 months.</td>
<td>There is no effect of oil intervention on the occurrence of AD at 12 months.</td>
</tr>
<tr>
<td>Superiority of the food intervention compared to no intervention as primary prevention of atopic dermatitis at 12 months.</td>
<td>There is no effect of food intervention on the occurrence of AD at 12 months.</td>
</tr>
<tr>
<td>Superiority of the food intervention compared to no intervention as primary prevention of food allergy at 36 months.</td>
<td>There is no effect of food intervention on the occurrence of food allergy at 3 years.</td>
</tr>
</tbody>
</table>
Babies were recruited at 18-week gestational age (GA week 16.0-21.6) and included into the mother-child cohort if they were born at a gestational age of at least 35.0 weeks. The interventions in this trial are carried out within the first 9 months of life and the outcomes are measured at separate time points (AD at 12 months and allergy at 36 months). The first publication, which will be written before the children are 36 months of age, will only investigate the first two primary hypotheses and focus on the primary endpoint of AD at 12 months. The second publication will be written after the children are 36 months of age and will investigate the remaining three primary hypotheses and focus on the primary endpoint of allergy at 36 months. All other efficacy analyses will be regarded as supportive or exploratory.

### 2.4.2 Decision Rule

This trial is designed to address two primary outcomes and five primary null hypotheses. Superiority is claimed if any of the primary null hypotheses are rejected on the significance level (alpha) of 0.05 (two-sided). The first two primary null hypotheses relate to the primary outcome of AD and will be addressed in one statistical model. The remaining primary null hypotheses relate to food allergy and will all be addressed in one statistical model.

### 2.5 Statistical Interim Analyses and Stopping Guidance

The original protocol states that interim analyses for both safety and efficacy were intended. However, after a later evaluation and discussions with the safety committee, this was considered not necessary for safety and subsequently not performed at any time point. Proposed interim analyses were not included in the clinicaltrials.gov registration.

### 2.6 Timing of Final Analysis
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The analysis for the primary outcome of AD at 12 months is planned when all babies have completed their 12-month visit, all data up to the 12-month visit have been entered, verified and validated and the primary database has been locked.

The analysis for the primary outcome of allergy at 36 months is planned when all babies have completed their 36-month visit, all data up to the 36-month visit have been entered, verified and validated and this updated version of the database has been locked.

2.7 Timing of Outcome Assessments
The target day and visits windows is defined in the protocol as:

<table>
<thead>
<tr>
<th>Visit or questionnaire Label</th>
<th>Target Day</th>
<th>Definition (Day window)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No suffix</td>
<td>18-week gestational age</td>
<td>16w0d-21w6d</td>
</tr>
<tr>
<td>week34mother</td>
<td>34-week gestational age</td>
<td>Questionnaire sent 16 weeks after inclusion to the first half of the study participants, onwards sent around 34 weeks of gestational age. No upper time limit</td>
</tr>
<tr>
<td>New-born</td>
<td>Birth (At randomization)</td>
<td>Filled in at inclusion Day 0-7</td>
</tr>
<tr>
<td>partus</td>
<td>Birth (From medical records)</td>
<td>Filled in later from medical record</td>
</tr>
<tr>
<td>baby3mdr</td>
<td>Doctor visit 3 months from birth</td>
<td>Target day + 14 days</td>
</tr>
<tr>
<td>quest3mdr</td>
<td>Questionnaire 3 months from birth</td>
<td>Questionnaire sent 3 months after birth. No upper time limit</td>
</tr>
<tr>
<td>baby6mdr</td>
<td>Doctor visit 6 months from birth</td>
<td>Target day +/- 28 days</td>
</tr>
<tr>
<td>quest6mdr</td>
<td>Questionnaire 6 months from birth</td>
<td>Questionnaire sent 6 months after birth. No upper time limit</td>
</tr>
<tr>
<td>ques9mdr</td>
<td>Questionnaire 9 months from birth</td>
<td>Questionnaire sent 9 months after birth. No upper time limit</td>
</tr>
<tr>
<td>baby12mdr</td>
<td>Doctor visit 12 months from birth</td>
<td>Target day +/- 28 days</td>
</tr>
<tr>
<td>quest12mdr</td>
<td>Questionnaire 12 months from</td>
<td>Questionnaire sent 6 months</td>
</tr>
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3 Statistical Principles

3.1 Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the corresponding treatment group or treatment interaction group difference will be denoted as statistically significant. All efficacy estimates will be presented with two-sided 95% confidence intervals. There are 5 primary null hypotheses to be tested in this trial. Due to the 2x2 factorial design, both interventions can be tested against any one primary outcome at the 5% significance level without correction for multiplicity.

The primary analysis of the outcome of AD assumes no intervention interaction effect and one can test sequentially at the 5% level (using a single statistical model): 1. The null hypothesis that neither intervention has an effect on the incidence of AD and if rejected 2. The null hypotheses that a. the skin care intervention has no effect on the incidence of AD and b. that the food allergy intervention has no effect on the incidence of AD.

The primary analysis of the outcome of food allergy makes no a priori assumption of the intervention effect and one can test sequentially at the 5% level (using a single statistical model): 1. The null hypothesis that neither intervention nor their interaction has an effect on the incidence of allergy and if rejected 2. The null hypotheses that a. the skin care intervention has no effect on the incidence of allergy and b. that the food allergy intervention has no effect on the incidence of allergy and c. that there is no interaction effect on the incidence of allergy.

3.2 Adherence and Protocol Deviations

3.2.1 Adherence to Allocated Treatment
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Adherence to the skin care intervention

The skin care intervention is self-reported by the mothers in weekly online diaries from week 2-26 of life. If less than 16/25 weeks is registered, the study participant is classified as not adherent.

Full adherence to the skin care intervention:

The protocol states that skin care should be performed at least 4 times a week.

The best 16 weeks of the weeks recorded in the diary should therefore document an average of at least 3.5 therapies per week in average, defined more specifically as:

1) At least 16 of 25 weekly diary entries reported at least an average of 3.5 oil-baths/week
2) at least 16 of 25 weekly diary entries reported at least an average of 3.5 Ceridal face cream applications/week.
3) In both cases, the following sequences of missing (NA)/0 are not permitted for full adherence (in the best 16 weeks:
   • 0-NA-NA
   • NA-0-NA
   • NA-NA-0
   • 0-0
   • NA-NA-NA
4) Both treatments have to be initiated by week 4
5) If treatment were stopped due to confirmed intervention related AEs in the intervention period, the subject is considered fully adherent
6) For Ceridal, if reported used “not as recommended”, this is considered 0

Early full adherence:

At least 10 weekly diary entries reported until week 18, an average of 3.5 oil-baths/week AND

1) At least 10 of 17 weekly diary entries reported at least an average of 3.5 oil-baths/week
2) at least 10 of 17 weekly diary entries reported at least an average of 3.5 Ceridal face cream applications/week.
3) In both cases, the following sequences of missing (NA)/0 are not permitted for full adherence (in the best 16 weeks:
   • 0-NA
   • NA-0
   • NA-NA
   • 0-0
4) Both treatments have to be initiated by week 4
5) If treatment were stopped due to confirmed intervention related AEs in the intervention period up to week 18, the subject is considered fully adherent

For Ceridal, if reported used “not as recommended”, this is considered 0
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To enable analyses of possible dose-response, we will analyze full adherence (oil bath + Ceridal) plus partial adherence (based upon oil-bath only) in four categories (total 5 categories):

Partial adherence to the skin care intervention:

1. At least 16 of 25 weekly diary entries reported at least an average of 3.5 oil-baths/week for oil-bath only.
2. Early partial adherence: At least 10 weekly diary entries reported until week 18, at least an average of 3.5 oil baths/week for oil-bath only.
3. 16 of 25 weekly diary entries with an average of between 2.5-3.4/week for oil-bath only.
4. 16 of 25 weekly diary entries with an average of between 1.5-2.4/week for oil-bath only.
5. 16 of 25 weekly diary entries with an average of between 0.5-1.4/week for oil-bath only.

Adherence to the food introduction intervention

Food adherence is assessed separately for each food. If less than 5/8 weeks between 19-26 weeks is registered, the study participant is classified as unknown. In this study we ordered the food interventions as following:

1. peanut  2. egg  3. wheat  4. milk

Options in the diary when answering days of tasting for each of the foods (peanut, milk, wheat and egg) in the last week:

0 dager (days)
1-2 dager (days)
3-5 dager (days)
Mer enn 5 dager (More than 5 days)
Vet ikke (Don’t know)

As a consequence, it is not possible to directly calculate the average number of days of tasting each of the foods.

Full adherence for each food (item 1-4):

Food introduced in weeks 13-18

AND

Reported ≥ 3-5 days/week in weeks 19-26, in the best 5 weeks

AND

At least 5/8 weeks available in weeks 19-26 (after introduction weeks)
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Partial adherence for each food (item 1-4):
1. Food introduced in week 13-18 AND at least 1-2 days/week (calculated from weeks 19-26), and not meeting fully adherent criteria.

Any documented food introduction:
Food introduced at least once in weeks 13-26 vs no recorded introduction

Visualisation

Display adherence of average oil bath and Ceridal used per week of the top 16 weeks separately.

Display percentage of introduction for each of the foods (item 1-4) at the right time (week 13-18)

Description of adherence per week for each of the foods (item 1-4)

Note that there are no adherence criteria defined for the subjects not receiving an intervention, as they were not given restrictions in skin care or food introduction.

We will display adherence by intervention group, separately for each of the different levels and skin/food categories. We will additionally list all reasons for stopping intervention and the age at stopping.

3.2.2 Protocol Deviations

The following are pre-defined major protocol deviations that may affect the efficacy of the intervention:

- Entering the trial when the eligibility criteria should have prevented trial entry
- Any participant without full adherence as defined in 3.2.1, unless the intervention was either not started due to a suspicion of possible allergy or stopped (in total or intermediate) due to a suspected adverse reaction and will only be reported for primary outcome for food allergy at 36 months investigation for the food interventions.
- Full adherence to an intervention the participant was not allocated to, with the exception of milk and wheat
- Missing primary endpoints

Protocol deviations are classified prior to statistical analysis of primary hypotheses for the atopic dermatitis outcome. The number (and percentage) of patients with major protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients that are included in the ITT (intention to treat) analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

3.3 Analysis Populations

The Enrolled set will include all participants who have provided informed consent and have been included into the study database.
STATISTICAL ANALYSIS PLAN for the PreventADALL Randomised Clinical Trial

The Full Analysis Set (FAS) will be defined as all participants randomly assigned to an intervention group via randomisation.

The Per Protocol Analysis Set (PPS) will include all randomised patients meeting the study eligibility criteria and with no major protocol deviations affecting the intervention efficacy.

Subgroup analysis on high-risk children defined as:

- Parental reported allergic disease: asthma, atopic dermatitis and/or allergic rhinitis.

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of screened patients and reasons for not entering the trial will be summarised and tabulated.

A CONSORT flow diagram (appendix A) will be used to summarise the number of patients who were:

- Included at 18 weeks of pregnancy
- Included and randomised at birth
  - Not included (reasons and n)
- Lost for primary outcome assessment
- Withdrew consent (n=1)
Withdrawal/Follow-up
The status of eligible and randomised patients at trial end will be tabulated by treatment group according to

- Attended at least one study visit
- withdrew consent

4.2 Baseline Patient Characteristics
The patient demographics and baseline characteristics to be summarised include:

- Mother’s age at 18 weeks (gestational age) inclusion
- Father’s age at 18 weeks (gestational age) inclusion
- Maternal BMI at inclusion
- Estimated Gestational Age at Birth (based upon femoral length at study enrolment)
- Study centre
- Mother’s Educational level
- Father’s Educational level
- Country of Origin (Mother)
- Country of Origin (Father)
- Marital Status
- Sex of baby
- Number of children living at home (full time or part time) (Q 8 in PreventADALL 18 ukers spørreskjema FINAL)
- Living Environment
- Mother Doctor Diagnosed Asthma
- Mother Doctor Diagnosed AD
- Mother Doctor Diagnosed Allergic rhinitis
- Mother Doctor Diagnosed Food allergy
- Mother Doctor Diagnosed Any Atopy
- Father Doctor Diagnosed Asthma
- Father Doctor Diagnosed AD
- Father Doctor Diagnosed Allergic rhinitis
- Father Doctor Diagnosed Food allergy
- Father Doctor Diagnosed Any Atopy
- Birth weight
- Length of Baby
- Cesarian section
- Previous deliveries
- Twins
- Dual pregnancy (two children from the same mother but separate pregnancies included)

Patient demographics and baseline characteristics will be summarised by randomised treatment arm and overall using descriptive statistics (N, mean, standard deviation for normally distributed variables, otherwise median, 25/75 percentiles, minimum, and maximum) for continuous variables, and number and percentages of patients for categorical variables. There will be no statistical analysis of potential differences between intervention groups. Any clinical important imbalance between the treatment groups will be noted.
5 Analysis

5.1 Outcome Definitions

5.1.1 General Definitions and Derived Variables

5.1.1.1 Atopic dermatitis

UK Working Party kriterier AD = Pt1 + at least 3 out of Pt2-5
Pt1. Kløende utsett, minst 4 uker (intermitterende eller sammenhengende) (Itchy rash, minimum 4 weeks (relapsing or chronic)
Pt2. Tidligere historie med utsett i hudfolder (albuer, knær, ankler, hals) eller på strekkeseide av underarm/legger (Previous history of rash in skin creases (elbows, knees, ankles, neck) or on extensor surfaces of arms/legs
Pt3. Allergisk rhinit hos patient og/eller atopisk sykdom hos 1. gradslinje (Allergic rhinitis and/or asthma in patient and/or atopic disease in first degree relative)
Pt4. Tørr hud siden fødsel (Dry skin since birth)
Pt5. Synlig fleksural dermatitt og/eller synlig dermatitt på underarme/legger UTEN affeksjon av axillar (Visible flexural dermatitis and/or visible dermatitis on arms/legs)

Hanifin & Rajka criterias for PreventADALL

A = Anamnestisk (må spørres etter) (History)

U = Ved Undersøkelsen (Examination)

Atopisk eksem (Atopic dermatitis) = 3 major + 3 minor

1. Kløe (A/U) (Pruritus)

2. Eksem til ansikt og/eller strekkeseide på armer/ben og/eller albuebøy/knehaser (U) (Dermatitis affecting flexural surfaces in adults and the face and extensors in infants)

3. Kronisk eller kronisk tilbakevennende eksem (A) (Chronic or relapsing dermatitis)

4. Familiær disposisjon for eksem, astma eller allergisk rhinit (A) (Personal or family history of cutaneous or respiratory atopy)

5. Tørr hud (minst 20% av hudoverflaten) (U) (Xerosis)

6. Ichthyose, palmar hyperlineariteit eller keratosis pilaris (U) (Ichthyosis, palmar hyperlinearity or keratosis pilaris)

7. Eksem på hender og/eller føtter (U) / Hand and/or foot eczema

8. Cheilitt (U) (Cheilitis)

9. Brystvorte eksem (U) (Nipple eczema)
10. Utsatt for hudinfeksjoner (min. 2 episoder med f.eks S.aureus, HSV, vorter, mollusker, dermatofyetter) (A) (Tendency toward cutaneous infections)

11. Ansiktsblekhet eller ansiktsserytem (U) (Facial pallor or facial erythema)

12. Perifollikulær aksentuering (U) (Perifolliclar accentuation)

13. Pityriasis alba (hypopigmenterte makler) (U)

14. Tidlig debut (før 5 års alder) (A) (Early age of onset)

15. Tilbakevennende konjunktivitt (mer enn 2 episoder) (A) (Recurrent conjunctivitis)

16. Mørke ringer rundt øyne (U) (Orbital darkening)

17. Infraorbitale folder (Dennie-Morgan linjer) (U)

18. Fremtredende fremre nakkefolder (U) (Anterior neck folds)

19. Eksemet forverres/blusser opp av emosjonelle- og/eller miljøfaktorer (A) (Emotional, environmental factors)

20. Eksemet forverres/blusser opp av mat (intoleranse/allergi) (A) (Intolerance to food)

21. Eksem/kløe forverres/blusser opp av svette (kløe) (A) (Itch when sweating)

22. Eksemet forverres/blusser opp av ull (Kløe) (A) (Intolerance to wool)

23. Hvit dermografisme (U) (white dermographism)

24. Positiv prikktest nå eller tidligere (mer enn 3mm) (A) (Positive SPT)

The primary outcome is a dichotomous variable (atopic dermatitis by 12 months) derived from the following variables:

- uk working party at 3 months (criteria 1 + at least 3 or more): rct_ad_outcome_ukwp@baby3mdr
- uk working party at 6 months (criteria 1 + at least 3 or more): rct_ad_outcome_ukwp@baby6mdr
- uk working party at 12 months (criteria 1 + at least 3 or more): rct_ad_outcome_ukwp@baby12mdr
- Hanifin Rajka (Minimum 3 from criteria 1 to 4 AND minimum 3 criteria from criteria 5 til 24 at 12 months): rct_ad_outcome_hrajka@baby12mdr

Atopic dermatitis (AD) by 12 months: rct_ad_outcome = positive for at least one of the 4 above

5.1.1.2 Food Allergy to the intervention food (peanut, milk, wheat and egg)

1. Food allergy by
   1. OFC positive
   2. No OFC now – OFC performed within last 6 months
   3. No OFC now – objective symptoms within 2 hours the last 6 months
   4. No OFC now – anaphylaxis last 2 years
2. Probable food allergy (no OFC performed)
   o Deemed by expert panel
   o Parents do not wish OFC
3. No food allergy
   o eaten + no symptoms (expert panel not involved)
   o SPT negative, no clinical reaction (expert panel not involved)
   o OFC negative
   o No OFC - Deemed by expert panel
4. Unclear
   o Deemed by expert panel

5.1.2 Primary Outcome Definition

The primary outcomes are

1. AD by 12 months of age diagnosed by either UK Working Party diagnostic criteria and/or Hanifin and Rajka diagnostic criteria at the 3-, 6- and/or 12-month follow-up investigations
   a. rct_ad_outcome is the dichotomous variable defining this outcome
   b. Intermediate variables are used to construct this:
      rct_ad_outcome_ukwp@baby3mdr, rct_ad_outcome_ukwp@baby6mdr,
      rct_ad_outcome_ukwp@baby12mdr rct_ad_outcome_hrajka@baby12mdr
2. Food allergy at 36 months of age for any of the four intervention foods (items 1-4; peanut egg, wheat, milk) as defined by the allergy expert panel (primarily, but not exclusively, based on OFC).

5.1.3 Secondary Outcomes Definitions

Secondary outcomes that will be analysed in the first paper (with AD primary outcome) are Possible atopic dermatitis (5.1.3.1) and onset of atopic dermatitis (5.1.3.2). All other secondary outcomes will be analysed at a later timepoint, and the appropriate variables will be defined prior to these analysis.

5.1.3.1 Possible Atopic dermatitis
Defined as itchy rash either present at 3,6 and/or 12 months visit and/or reported by questionnaire at 3,6,9 and/or 12 months.

Presence of clinical eczema an itchy rash for the last 4 weeks at visit is registered in the following questionnaires:

- 3 months: PreventADALL 3 mdr visit REG FINAL: Q8a) eksem (Skin_examination=2)
- 6 months: PreventADALL 6 mdr visit REG FINAL: Q 13b) Pt1 (Crit. 1 in UKWP)
- 12 months: PreventADALL 12 mdr visit REG FINAL: Q 12b) Pt1 (Crit. 1 in UKWP)
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Itchy rash during the last 3 months for 4 weeks or more is registered in the following questionnaire:

- 3, 6, 9 and 12 months in PreventADALL Q 3-6-9-12 mo FIN:AL: Q 21 c) i Ja

Any of the following is positive:
- uk working party at 3 months (criteria 1): rct_possible_ad_outcome_ukwp@baby3mdr
- uk working party at 6 months (criteria 1): rct_possible_ad_outcome_ukwp@baby6mdr
- uk working party at 12 months (criteria 1): rct_possible_ad_outcome_ukwp@baby12mdr

Reported itchy rash at 3 month: rct_possible_ad_outcome_itchy_rash@baby3mdr
Reported itchy rash at 6 month: rct_possible_ad_outcome_itchy_rash@baby6mdr
Reported itchy rash at 9 month: rct_possible_ad_outcome_itchy_rash@baby9mdr
Reported itchy rash at 12 month: rct_possible_ad_outcome_itchy_rash@baby12mdr

Variable for possible AD ever derived from the above (including those that also have a verified AD diagnosis): rct_possible_ad_outcome

Note: Some participants have a diagnosis of AD without classifying for the possible AD diagnosis

5.1.3.2 Onset of possible atopic dermatitis
The onset of possible or established AD up to 12 months of age defined as the first appearance of possible AD by the variables in 5.1.3.1.

5.1.3.3 Recurrent bronchial obstruction

1. a minimum of two episodes of wheeze between 0 and 12 months of age
2. a minimum of 3 episodes of wheeze between 0 and 24 months of age
3. a minimum of 3 episodes of wheeze between 0 and 36 months of age.

5.1.3.4 Allergic sensitisation

Allergic sensitization 0-12 months of age based upon the following:

<table>
<thead>
<tr>
<th>s-IgE (kU/L) &amp;/or Phadiotop infant (iU/l)</th>
<th>Skin prick test (mm &gt; negative control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sensitization:</td>
<td>slgE &lt; 0.10</td>
</tr>
<tr>
<td>Possible sensitization:</td>
<td>slgE 0.10 - 0.34</td>
</tr>
<tr>
<td>Allergic sensitization:</td>
<td>slgE ≥ 0.35</td>
</tr>
</tbody>
</table>

Further, based upon consistent observations that sensitisation to more than one allergen is associated with more severe disease (following the secondary outcome):

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Polysensitization: allergic sensitisation to more than one allergen.

5.1.3.5 Food allergy to any other food allergen

Doctor diagnosed food allergy to any food allergen other than egg, milk, wheat or peanut.

5.1.3.6 Anaphylaxis

Doctor diagnosed anaphylactic reaction to any allergen

5.1.3.7 Rhinitis
The allergic rhinitis definition will be further specified/adjusted based upon current knowledge prior to analyses in 2020.
5.2 Analysis Methods

5.2.1 Primary Outcome

5.2.1.1 Primary Analysis
Primary outcome: Atopic dermatitis by 12 months

The occurrence of atopic dermatitis by 12 months (dichotomous) will be analysed using a mixed effects logistic regression model with oil bath treatment as a dichotomous fixed effect, food treatment as a dichotomous fixed effect, the interaction of the oil bath and food treatments as a fixed effect, and randomisation “bydel” and randomisation “yearly quarter” as a random effects, assuming an unstructured correlation structure for the random effects. The main effect of oil bath treatment and the main effect of food intervention treatment are the principle parameters of interest. If the model fails to converge, then the random effects will be dropped from the model and a logistic regression will model will be fit instead.
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Missing primary outcome data will be imputed with the best-case option, no AD. It is assumed that children with AD are most likely to attend the follow up investigations, while children without any disease are most prone not to prioritize to attend.

Primary outcome: Food allergy by 36 months

The occurrence of food allergy by 36 months (dichotomous) will be analysed using a mixed effects logistic regression model with oil bath treatment as a dichotomous fixed effect, food treatment as a dichotomous fixed effect, the interaction of the oil bath and food treatments as a fixed effect, and randomisation “bydel” and randomisation “yearly quarter” as a random effects, assuming an unstructured correlation structure for the random effects. The main effect of oil bath treatment and the main effect of food intervention treatment and the interaction of the oil bath and food treatments are the principle parameters of interest. If the model fails to converge, then the random effects will be dropped from the model and a logistic regression will model will be fit instead.

Missing primary outcome data will be imputed with the best-case option, no FA. It is assumed that children with FA are most likely to attend the follow up investigations, while children without any disease are most prone not to prioritize to attend.

5.2.1.2 Summary Measures
Descriptive statistics will include number and percentage by treatment group. Descriptive statistics will be based on non-imputed data, thus the number of evaluable outcome measurements at the time of primary interest (at 12 months for atopic dermatitis and at 36 months for food allergy) will also be presented.

The primary effect estimate will be the adjusted risk difference, computed from the logistic regression effect estimate using the delta method. The adjusted relative risk will also be reported together with the p-value of the null-hypothesis test of no treatment difference from the logistic regression. If the 95% confidence interval of the adjusted risk difference does not include 0, the number needed to treat, calculated as the reciprocal of the adjusted risk difference will be reported.

5.2.1.3 Assumption Checks and Alternative Analyses
Since the logistic model does not include continuous covariates, there are no major model checks needed.

5.2.1.4 Missing Data
For the primary outcome, missing data occur if a patient has not completed the study within the time window of the final visit (52 ± 4 weeks).

In the primary analysis, missing binary outcome data will be imputed with the best-case imputation (e.g. no AD).

5.2.1.5 Sensitivity Analyses
1) Restricting the primary analysis to the PPS
2) Adjusted analysis (logistic regression adjusting for family history and sex
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3) Missing outcome imputed using multiple imputation by chained equations under the assumption that missing data values are likely to be missing-at-random. 15 imputed data sets will be drawn separately for each randomised group. All baseline variables, primary outcome variables and available binary or continuous secondary outcome variables will be used in the imputations.

4) Missing outcome handling with worst case imputation.

5) Complete case analysis

6) Same as the primary analysis model but with the interaction term removed.

5.2.1.6 Subgroup Analyses
Subgroup analysis of the primary outcome will be performed for family history of AD (yes/no) and maternal fialagrin mutation when available. The subgroup analysis will be done by adding subgroup and treatment-subgroup interaction terms to the mixed logistic regression model.

5.2.2 Dichotomous Secondary Outcomes

5.2.2.1 Main Analysis
Same as for the Primary outcome

5.2.2.2 Summary Measures
Same as for the Primary outcome

5.2.2.3 Assumption Checks
Same as for the Primary outcome

5.2.2.4 Missing Data
Same as for the Primary outcome

5.2.2.5 Sensitivity Analyses
Same as for the Primary outcome

5.2.2.6 Subgroup Analyses
Same as for the Primary outcome

5.2.3 Continuous Secondary Outcomes

Not applicable

Time to event secondary outcomes

5.2.3.1 Main Analysis

Time-to-event outcomes will be modelled using interval censoring methods using a parametric survival regression model assuming non-informative censoring and regular observation times.

5.2.3.2 Summary Measures
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Adjusted hazard ratios will be presented.

5.2.3.3 Assumption Checks

The fit of the model will be investigated using residual plots and other graphical methods.

5.2.3.4 Missing Data

Missing data will be handled directly by the method which handles censored data.

5.2.3.5 Sensitivity Analyses

Same model but with family history and sex as covariates

5.2.3.6 Subgroup Analyses
Same as for the primary outcome.

5.2.4 Additional Analyses

6 Safety Analyses

6.1 Adverse Events
Adverse events are recorded in

1. Weekly diaries (internet forms) from age 2 to 26 weeks
2. Quarterly internet queries (3, 6, 9 and 12 months of age)
3. Adverse events forms registered by study personnel

6.1.1 Serious Adverse Events
Recorded in designated adverse event forms

Serious adverse events include

- Death
- Hospitalizations
- Anaphylaxis

6.1.2 Other adverse events

6.1.2.1 Recorded in weekly diaries from 2 to 26 weeks of age
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General:
- Dry skin
- Itching
- Rash (red) in face, arms or legs
- Urticaria
- Facial swelling
- Vomiting
- Severe cough
- Respiratory distress

Related to food intake:
- Facial rash
- Urticaria
- Facial swelling
- Itching rash (not urticarial)
- Stomach pain
- Vomiting or diarrhoea
- Respiratory distress
- Sever cough

6.1.2.2 Recorded in quarterly (3, 6, 9 or 12 months of age) queries
Symptoms:
- Any illness (yes/no)
- Upper airway infection
- Conjunctivitis
- Otitis
- Throat infection
- Croup
- Fever without specific cause
- Influenza type illness
- Gastroenteritis
- Urinary tract infection
- Unspecified viral infection
- Bronchitis
- Bronchiolitis/RSV
- Pneumonia
- Other lower respiratory infection
- Colic
- Other stomach pain
- Pain or other discomfort leading to seeking health care
- Febrile seizures
- Non-febrile seizures
Physician attendance

- Medical condition – number of times
- Accident/injury – number of times
- Hospitalizations, due to
  - Allergic reaction
  - Atopic dermatitis
  - Croup
  - Bronchiolitis
  - Pneumonia, bronchitis or other respiratory disease
  - Influenza
  - Gastroenteritis
  - UTI
  - Unspecified infection
  - Febrile seizures
  - Non-febrile seizures
  - Intoxications
  - Foreign body ingestion/inhalation
  - Surgery
  - Accident or injury
  - Other

Reported suspected reaction to any of the four intervention food items

- Rash/dermatitis
- Oral itching
- Swollen lips/eyes
- Urticaria
- Vomiting or stomach pain
- Respiratory distress

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6.1.2.3 Recorded in adverse event forms
Adverse events that have led to discontinuation of the intervention will be of main interest.

Data are reported by the following:

<table>
<thead>
<tr>
<th></th>
<th>Bath oil</th>
<th>Ceridal</th>
<th>Peanut</th>
<th>Milk</th>
<th>Egg</th>
<th>Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopping (yes/not reported)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of stopping reported first time(days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason(s) for stopping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Possible reasons for discontinuation of skin intervention from the AE-form:

- Infantile seborrheic dermatitis
- Folliculitis/Infantile acne
- Worsening of AD
- Unspecific skin reaction
- Other

Possible reasons for discontinuation of food (peanut/milk/wheat/egg) intervention from the AE-from:

- Verified IgE-mediated food allergy
- Suspected food allergy
- Other

Additionally, we will record potential AEs based upon the following variables:

- Slippage accident

6.1.2.4 Recorded in 3 months investigation form
1) For peanut, if children reacted to peanuts after the first exposure, this will be reported from the 3-month clinical investigation form.

6.1.2.5 Reporting of adverse events and what types of tables should we make
The following will be reported:

- number of adverse events, by time (week or quarter of a year, see above) and intervention group
  - Bar charts with time on the x-axis, 4 intervention groups per time point
  - One panel of charts for each organ system, with specifics stacked in charts
- proportion of patients with adverse events, by intervention group.
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Serious adverse events will be reported in the same way described as above.

The following will be reported for adverse event leading to treatment discontinuation:

- Number of adverse events possibly related to treatment and leading to discontinuation.

A table of most the common adverse events (>2%) and all serious adverse events will be generated.

7 Statistical Software

All statistical analyses will be done in R version 3.5.2.

8 References

8.1 Literature References


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8.2 Reference to Data Handling Plan

8.3 Reference to the Trial Master File and Statistical Documentation

8.4 Reference to other Standard Operating Procedures or Documents

9 Appendices

9.1 Appendix 1 randomization bydels used
Alna bydel
Bjerke bydel
Frogner bydel
Gamle Oslo bydel
Grorud bydel
Grunerløkka bydel
Nordre Aker bydel
Norstrand bydel
Sagene bydel
St. Hanshaugen bydel
Stovner bydel
Søndre Nordstrand bydel
Ullern bydel
Vestre Aker bydel
Østensjø bydel

Aurskog-Høland
Enebakk
Fet
Frogn
Gjerdrum
Gran
Hole
Hurdal
Hurum
Jevnaker
Lier
Lunner
Modum
Nannestad
Nedre Eiker
Nes
Nittedal
Rælingen
Røyken
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Sørum
Ullensaker
Vestby
Øvre eiker
Ås

Asker
Bærum
Drammen
Eidsvoll
Kongsberg
Lørenskog
Nesodden
Oppegård
Ringerike
Skedsmo
Ski
Andre

Hägersten-Liljeholmen
Enskede-Årsta Vantör
Farsta
Skarpnäck
Södermalm/Gamla Stan
Bromma
Hässelby-Vällingby
Spånga-Tensta
Rinkeby-Kista
Östermalm
Norrmalm
Kungsholmen
Solna
Sundbyberg
Upplands Väsby
Järfälla
Märsta
Bro/Kungsängen
Lidingö
Nacka
Huddinge
Sigtuna
Ekerö
Sollentuna
Other

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Fredrikstad
Sarpsborg
Halden
Råde
Hvaler
Skiptvet
Hobøl
Aremark
Eidsberg
Marker
Spydeberg
Trøgstad
Rakkestad
Moss
Våler
Rygge