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Different potencies of topical corticosteroids for a better treatment strategy in children with atopic dermatitis (the Rotterdam Eczema study): protocol for an observational cohort study with an embedded randomized open-label controlled trial

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Manuscripts

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3 **Different potencies of topical corticosteroids for a better treatment strategy in**
4 **children with atopic dermatitis (the Rotterdam Eczema study): protocol for an**
5 **observational cohort study with an embedded randomized open-label controlled**
6 **trial**
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30 G. Elshout, A.M. Bohnen and P.J.E. Bindels conceived the idea and secured funding.
31 Ethics applications were made by K.F. van Halewijn in collaboration with G. Elshout,
32 A.M. Bohnen and P.J.E. Bindels. S.G.M.A. Pasmans and P.J. van den Berg provided
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1 2 3 Trial registration

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5 This trial was prospectively registered at the Netherlands National Trial Register (NTR:
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7 6679).

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11 Abstract

12
13 Introduction

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15 Topical corticosteroids (TCS) of different potencies are the main treatment to control
16 atopic dermatitis (AD). The Dutch guideline on AD for general practitioners (GPs)
17 recommends a stepwise approach in which treatment steps are tailored to the severity
18 of the disease, starting with the lowest possible potency of TCS. (1) However, it remains
19 unclear whether the recommended stepwise approach is most efficient. This
20 randomized open-label controlled trial aims to determine whether a potent TCS is more
21 effective than a low-potency TCS in the initial treatment of children with a moderate
22 flare-up of AD in primary care. In the observational cohort, the overall aim is to
23 determine the frequency, burden and determinants of flare-ups of AD during follow-up.
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32 Methods and Analysis

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34 The study is an observational cohort study with an embedded pragmatic randomized
35 controlled, open-label trial. Eligible are patients diagnosed with AD (aged 12 weeks to
36 18 years) who visited the GP for AD, or received repeated prescriptions for AD in the
37 previous 12 months; follow-up of the cohort is 1 year. Children are enrolled in the trial if
38 they have a flare-up of AD during follow-up in the cohort. Eligible children are
39 randomized to the intervention group (with a potent TCS once daily) or to the GP
40 guideline group (with a low potency TCS once daily). Primary outcome is the difference
41 in average subjective disease severity over 24 weeks follow-up in the trial, measured
42 with the Patient Oriented Eczema Measure (POEM). As secondary outcome, the
43 Eczema Area and Severity Index (EASI) is measured.
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53 Ethics and Dissemination

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55 This study tests the hypothesis that immediate treatment with a potent TCS during a
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flare-up of AD leads to faster and more efficacious results as compared to starting with a TCS with low potency with less overall use of TCS.

Trial registration

This trial was prospectively registered at the Netherlands National Trial Register (NTR) under number 6679.

Keywords

Primary care, paediatrics, atopic dermatitis, cohort, randomized open-label controlled trial

Strengths and limitations of this study

- This is the first study to investigate the effectiveness of initial treatment with TCS class I vs class III for long-term control of atopic dermatitis in children in primary care.
- Pragmatic treatment strategy in real-life clinical practice.
- Study is performed in general practice, where most children with eczema are treated.
- Cohort study on determinants of flare-up and disease burden of atopic dermatitis in children.
- This randomized open-label trial may be prone to observation bias.

Introduction

Atopic dermatitis (AD), or eczema, is a chronic, highly pruritic inflammatory skin disease and one of the most common skin disorders in children. (2) Eczema is in the top 10 of the most prevalent disorders in general practice in children aged up to 18 years.(3) The prevalence of AD has increased over the past 30 years.(4) It is estimated that 10-20% of children and 1-3% of adults in developed countries are affected by the disorder.(5) In the Netherlands, cumulative incidence of AD at age 18 years is at least 24%. (6) AD often starts in early infancy; about 45% of all cases begin within the first 6 months of life, 60% during the first year, and 85% before 5 years of age.(7) AD is associated with (later) occurrence of asthma and allergic rhinitis.(6)

The disorder results in significant morbidity and adversely affects quality of life. Factors that contribute to a poor quality of life are fatigue, itch, activity restriction, depression, and sleep deprivation.(8) Approximately 47-60% of children with AD experience sleep disturbance, (9) and children with AD and their parents can lose about 1-2 h of sleep/night.(10) Therefore, AD affects social functioning and psychological wellbeing, and has an even greater impact than diabetes on families of young patients. (10, 11) This includes direct and indirect financial costs, time spent on treatment, sleep deprivation (1-2 h/night) and physician visits.

Since there is no definitive cure for eczema, suppressive treatment aims to control the disease. The majority of patients in general practice control their symptoms by application of emollients accompanied by symptomatic anti-inflammatory therapy consisting of topical corticosteroids (TCS). (12) The Dutch guideline on AD for general practitioners (GPs) advocates a stepwise approach in which treatment steps are tailored to the severity of the disease, as determined using the Three Item Severity (TIS) score. (1) The choice of potency of corticosteroids is determined by estimating the required effect. When AD is mild to moderate, a mild (class I) to moderate potent (class II) TCS is preferred, while potent (class III) TCS is used only when AD is severe. When treatment is insufficient, a higher class can be used. Due to safety concerns, the Dutch

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3 GP guideline recommends to use the lowest potency possible that will still be effective
4 to treat the eczema. Potential local side-effects of CS are telangiectasia, atrophy,
5 hypopigmentation, and striae. However, the review of Siegfried et al. showed no
6 evidence of atrophy and supported the long-term safety of low and moderate TCS. (13)
7 Potential systemic effects of TCS may include suppression of the hypothalamic-
8 pituitary-adrenal (HPA) axis, and osteoporosis, glaucoma, cataract, and growth
9 reduction. Nevertheless, osteoporosis and growth reduction are not reported in studies
10 with long-term follow-up. (13-15).

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12 The existing trials on the efficacy of TCS in children are often outdated and of inferior
13 quality with only a short follow-up. (16-18) However, they indicate that more potent TCS
14 may result in faster and better disease control in AD; nevertheless, it is not clear which
15 initial treatment strategy (i.e. mild or potent CS) is the best. (1, 19) During a flare-up,
16 treatment with a potent TCS might lead to faster and better results as compared to
17 starting with a mild TCS, with eventually less overall use of TCS. Besides improvements
18 in disease control and patients' satisfaction, this may also lead to fewer medical
19 consultations and prescriptions, and may therefore be more cost effective. The present
20 study focuses on these gaps and hopes to make an important contribution to knowledge
21 regarding the use of TCS in children with AD treated in general practice.
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34 35 **Objectives**

36 To determine whether initial treatment with a potent TCS is more effective than a mild
37 TCS in the treatment of children with a moderate flare-up of AD in primary care in the
38 short (i.e. 1 week and 4 weeks of follow-up) and long-term (i.e. 6 months follow-up)
39 control of the disease.
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42 In the observational cohort, the aim is to determine the frequency and determinants of
43 flare-ups of AD. Furthermore, we will explore the burden of AD by measuring severity,
44 medication use, healthcare use and quality of life (QoL) during 1-year follow-up.
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47 48 **Study design**

49 The Rotterdam Eczema study is an observational cohort study with an embedded
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3 pragmatic randomized open-label superiority trial with two groups and a patient-reported
4 primary outcome of long-term control.
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9 Methods; participants, interventions and outcomes

10 Healthcare system

11 The GP plays a key role in the Dutch healthcare system and (almost) everybody is
12 registered with a GP practice. Diagnosis and treatment of eczema, also in children, are
13 part of general practice. In case of diagnostic or treatment problems in children with
14 eczema, referral to secondary care is available; however, referral to a dermatologist is
15 not possible without the consent of a GP.
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20 Study setting

21 Children will be recruited from general practices located in the western part of the
22 Netherlands. The GPs will perform a search in their information system to identify
23 potentially eligible children.
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29 Eligibility criteria

30 To be eligible to participate in the cohort study, a child must meet all of the following
31 criteria: aged between 12 weeks and 18 years, diagnosis of eczema (ICPC code S87
32 and S88 or prescription of topical treatment for eczema) plus confirmation of the
33 diagnosis by the GP, a consultation or repeated prescription in the previous 12 months,
34 and informed consent. Exclusion criteria for the cohort study are: as determined by the
35 GP (e.g. family problems), currently under treatment with a dermatologist, contra-
36 indications for the study medication, language barrier, or no access to internet
37 (necessary to fill in weekly online questionnaire).
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47 The inclusion criteria for the trial part of the study are: participation in the cohort, flare-
48 up (i.e. need to intensify topical treatment) from the child's and/or parents' point of view,
49 a Three Item Severity (TIS) score from ≥ 3 to < 6 . Exclusion criteria for the trial part are:
50 use of TCS in the 2 weeks before inclusion in the trial, AD on eyelid(s), $> 50\%$ of body
51 affected by AD, other skin disorders hampering proper assessment of eczema,
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3 pregnancy and or breastfeeding, or untreated skin infections (bacterial, viral, fungal or
4 parasitic).
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Interventions

10 Eligible children will participate in the trial part if they have a flare-up of AD. They will be
11 randomized to either the **intervention group** or to the GP guideline group (**control**
12 **group**). Those allocated to the intervention group will receive a potent TCS class III
13 once daily to start with at each flare-up during the follow-up period of the trial. If children
14 are aged >2 years, they will follow a predefined weaning-off scheme (i.e. reduction of
15 frequency) when their symptoms have improved. If children are aged <2 years, they will
16 be reassessed by the GP after 1-2 weeks. When AD is improved but still needs
17 treatment, children will be treated according to the Dutch GP guideline (i.e. switch to a
18 less potent TCS).
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26 Children in the control group will receive care as stated in the Dutch GP guideline for all
27 flare-ups during the trial period. First, they will start with a mild TCS class I once daily.
28 When not improved within 1-2 weeks, a mild potent TCS class II once daily will be
29 prescribed. When class II does not improve symptoms within 1-2 weeks, a potent TCS
30 class III will be prescribed once daily. When symptoms do improve, children will follow a
31 predefined weaning-off scheme. (1)
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36 In the present study, hydrocortisone acetate cream 1%, and triamcinolone acetonide
37 cream 0.1% will be used as class I and class II TCS, respectively, since this is a
38 recommended preparation in the national guideline.(1) For class III TCS, fluticasone
39 propionate cream 0.05% will be used; this cream was chosen since it has a relatively
40 short half-time as compared to the class III TCS recommended by the national guideline
41 (i.e. betamethasone).(1) and is expected to limit potential side-effects. Children will
42 receive the prescription from their own GP and will obtain the prescribed medication
43 from the child's own pharmacy.
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50 Besides the use of corticosteroids, all children (control and intervention group) will
51 always be advised to use indifferent therapy with a standard emollient (i.e.
52 'cetomacrogol'). The advice is to use the emollients daily.
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Figure 1. Flow chart of the study.

Outcomes

Primary outcome measure

The primary outcome will be change in disease severity over 24-weeks follow-up in the trial, as measured by the average score of the Patient-Oriented Eczema Measure (POEM). POEM is a patient-reported outcome based on symptoms over the previous week, which can be self-completed by the child's parent or the child. POEM is a validated questionnaire and has been recommended by the Harmonizing Outcome for Eczema (HOME) initiative as the preferred instrument to capture patient-reported symptoms in eczema trials.(20) The POEM score is collected weekly in the trial part over 24 weeks and, to measure long-term control, the difference between the two treatment groups in the average POEM scores will be measured over these 24 weeks.

Secondary outcome measures

The Eczema Area and Severity Index (EASI) will be used as objective measurement of the AD. The EASI has been identified by the HOME initiative as the core outcome measurement instrument to evaluate clinical signs of AD in all future trials investigating interventions for AD. (21) The EASI is scored by a physician and rates both the intensity and extent of AD signs. The EASI will be used as secondary outcome in both the trial and the cohort study. The EASI score is collected at baseline, and at weeks 1, 4 and 24 of the trial, and at baseline, and at weeks 26 and 52 in the cohort study.

Other secondary outcomes in the trial part include: i) changes in disease severity after 1 week and 4 weeks using POEM, ii) QoL using the Infants' Dermatitis Quality of Life Index (IDQOL) or Children's Dermatology Life Quality Index (CDLQI) (depending on age), iii) medication compliance (determined as a POEM >8 and use of TCS during that week), iv) local side-effects (painful application, telangiectasia, atrophy, hypopigmentation, and striae), v) time to recovery (i.e. time till start weaning-off treatment), vi) frequency of flare-ups, vii) medication use (subjective and objective), viii) patient global assessment and investigator global assessment (both on a 6-point scale;

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3 clear, almost clear, mild, moderate, severe, very severe), ix) itch intensity score (the
4 numeric rating scale-11 is ranging from 0, no itch to 10, worst itch imaginable), and x)
5 healthcare use (i.e. telephone contact with GP, consultation at the general practice, or
6 referral to secondary care).
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10 The QoL questionnaires are the IDQOL and CDLQI: both are validated and widely used
11 in dermatology as a QoL scale for children aged ≤4 years and aged 4-16 years,
12 respectively. (22, 23). The use of medication will be registered by weighing the tube of
13 TCS after 1 week, 4 weeks and 24 weeks in the trial. Furthermore, in the weekly
14 questionnaire, the children will register the amount of days that TCS and neutral
15 ointment were used in the previous week.
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18 The aim of the observational cohort is to determine the frequency and determinants of
19 flare-ups of AD after 1-year follow-up.
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22 Secondary outcomes concerning the cohort includes disease severity at inclusion, and
23 at 26 weeks and 52 weeks follow-up using POEM and EASI, QoL, frequency of flare-
24 ups, medication use, and healthcare use.
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31 Table 1. Schedule of observations made during the study.

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36 **Sample size**

37 In this study, we based our sample size calculation on the minimal clinically important
38 difference (MCID) of the POEM in young children with eczema as determined by Gaunt
39 at al.(24) The MCID is the smallest change in an outcome measure that represents a
40 clinically relevant outcome. A treatment effect of 3.0 POEM points was considered
41 clinically relevant. We used a mean of 128.8 (SD of 5.9) as presented in trials with a
42 similar population (i.e. primary care patients) on baseline POEM characteristics. (24)
43 Taking these numbers into account, with a power of 80% and $\alpha=0.05$ (2-sided) we need
44 61 children per trial group. Assuming a dropout rate of 15% during the study, 72
45 children per treatment arm are required.
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Recruitment

Based on Dutch GP data and an expected patient participation of 50%, per participating GP we expect to include 7 children per year for the cohort, and 4 in the trial (based on flare-ups). (3) Therefore, we expect to need about 36 participating GPs. First, we will collaborate with our academic network named PRIMEUR. The academic PRIMEUR network includes 13 centers with about 97 participating GPs and about 160,000 patients. If the inclusion is behind expectations, more GPs will be invited to participate in the study. Furthermore, if inclusion still remains behind expectations using the search protocol (e.g. consultation, or repeated prescription in the previous 12 months) we will expand the search period from 12 to 24 months.

Children will be recruited from general practices. When a GP decides to participate, the GP will perform a search in their information system to identify all possible eligible children. Invitation letters to participate (in the name of the GP) will be sent to the parent/carer of the children.

Children are asked to respond using a response card or response e-mail, irrespective of whether or not they are willing to participate. These responses are sent to the coordinating researcher of the department of General Practice, Erasmus Medical Center Rotterdam.

After receiving a positive response from the child, the research assistant will have telephone contact with the child (this can be with the parents if the child is aged ≤ 12 years, or the children themselves). During this telephone contact, additional information on the study and study procedures will be explained. Based on the telephone contact, if the child is eligible and is still interested in participating, the patient information letter (PIF) will be sent by mail. Afterwards, if the child is willing to participate, the informed consent will be signed by the parents (if the child is aged ≤ 16) or the child (when aged ≥ 12 years) and sent to the department of General Practice.

After receiving the signed PIF, the research assistant will contact the general practice of the child to inform them about the child's participation. The GP practice will contact the parents of the child to arrange a consultation. During this first consult with the physician assistant, the baseline EASI will be obtained.

Assignment of interventions

When the AD flares up, the child (or the child's parents) has to make an appointment by the GP. The definition of a flare-up is the need to intensify topical treatment from the patient's and/or parents' point of view

If the child has a flare-up of AD and is eligible for inclusion in the trial, the child will be randomly allocated to one of the two groups by the physician assistant of their own GP, using the data management system (Research manager). The randomization list will be computer-generated and unknown to the investigators.

Children will be stratified by TIS score (i.e. TIS score 3, 4 and 5) to ensure equal distribution of the severity of AD between the intervention and control group. Random permuted blocks of two will be generated. The GP will prescribe the medication of randomization.

Data collection and methods

Data collection of the patient-reported outcomes and the objective reported outcomes will be carried out using online case report forms. Children (or the child's parents) will receive a reminder by email if questionnaires are not filled in after a standardized interval of three days. If questionnaires are not filled in at key time points, participants will receive a telephone reminder. Children will receive a small gift after completing the cohort or trial follow-up.

The physician assistants will receive additional training in the pathophysiology and treatment of AD and in scoring the EASI.

Data management

Data will be handled confidentially and anonymously. A child's identification code is used to link the data to the child; a unique code is randomly generated for each individual. The principal investigator safeguards the key to the code.

The software program Research Manager will be used for the online questionnaires and the childrens' personal data, respectively.

Statistical methods

All analyses of the primary study parameters will be performed according to the intention-to-treat principle (ITT), i.e. irrespective of compliance. Those who perform the analyses will be kept blind regarding which group has received what kind of treatment.

Secondary, a per-protocol analysis, excluding children in whom major violations of the protocol have occurred, will also be performed. Major protocol violations are: withdrawal from study or loss to follow-up, and medication compliance <75%.

In case major events occur during the study period that necessitate withdrawal from study, or loss-to-follow-up/dropout for other reasons, weekly diary card data will be evaluated up to the week of such dropout. However, children are requested to agree with further follow-up according to the study protocol (e.g. weekly questionnaires).

Medication compliance <75%, (also called non-compliance) is determined as a POEM >8 and no use of TCS during that week; the compliance is determined per week.

For the primary outcome, statistical comparison between the treatment groups will be done using analysis of covariance (ANCOVA) including the covariates: baseline symptom score, age, and gender. Treatment effects will be tested two-sided with a significance level of 5%.

For the main study parameter, it is essential that the weekly diaries are filled in adequately. However, in case of missing data, these will be imputed using multiple imputation; this is considered the most appropriate way of dealing with missing data.

(25) Missing values of the POEM will be imputed 10 times using the multivariate imputation by chained equations (MICE) logarithm (R-Project). The imputation model included sex, age, type of medication used and frequency of application, and the outcome measure POEM.

Secondary outcomes of the trial, statistical comparison between the treatment groups for changes in disease severity, and QoL after 1 week and 4 weeks, will be performed using ANCOVA, including the covariates baseline symptom score, age and gender. The other secondary outcomes (i.e. local side-effects, systemic side-effects, compliance, frequency of flare-ups, medication use and healthcare use) will be analyzed with linear or logistic regression when appropriate. For the time to recovery, Cox regression analyses will be performed.

To explore differences in patient and disease characteristics in the two treatment arms, and to determine which factors are related to compliance to the two treatment strategies, backward logistic regression will be used.

Patient characteristics to be examined are: age, sex, age at presentation of AD, history of atopy (i.e. asthma, allergic rhinitis, food allergy and anaphylaxis), use of other CS (i.e. nasal, inhaled, oral), and QoL (IDQoL, CDLQI). Disease characteristics are disease severity (POEM and EASI), duration of AD, location of AD (i.e. head and neck, upper limbs, lower limbs and trunk, all extracted from EASI) and previous medical care (i.e. no previous treatment, GP only, GP and secondary care).

To explore which factors are related to compliance to the two treatment strategies, backward logistic regression will be used. The factors to be explored are treatment arm, age, sex, age at presentation of AD, disease severity (POEM and EASI), duration of AD, use of other CS (i.e. nasal, inhaled, oral), and QoL (IDQoL, CDLQI).

The secondary outcomes for the cohort will be analyzed with descriptive statistics (i.e. disease severity, frequency of flare-ups, medication use, healthcare use, QoL). Analyses to determine what the determinants of flare-ups of AD are after 1-year follow-up will be performed with logistic regression analyses.

Ethics and dissemination

The study protocol is approved by the Medical Ethics Committee (MEC) of the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2017-328).

Amendments are changes made to the research protocol after a favorable opinion from the accredited MEC. All substantial amendments will be notified to the MEC and to the competent authority.

The results of the study will be published in international peer-reviewed journals and presented at (inter)national conferences. We aim to publish several peer-reviewed publications on the best treatment strategy in children with AD related to patient-oriented outcomes, healthcare consumption, and side-effects. The results of this study may be implemented into clinical practice and/or can be used for the next update of the Dutch guideline on AD for GPs.

1 2 3 4 5 Safety reporting 6 7

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9 In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the
10 study if there is sufficient ground that continuation of the study will jeopardise subject
11 health or safety. The sponsor will notify the accredited METC without undue delay of a
12 temporary halt including the reason for such an action. The study will be suspended
13 pending a further positive decision by the accredited METC. The investigator will take
14 care that all subjects are kept informed.
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18 **Monitoring**
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20 Due to the characteristics of this study it is not necessary to install a Data Safety
21 Monitoring Board. Nevertheless, the study will be monitored as described in the ICH-
22 GCP Guidelines (chapter 5.18). The department of General Practice has developed a
23 monitoring plan and monitoring checklist (based on the ICH-GCP Guidelines) which will
24 be used in this study. A senior researcher (project leader) will be designated as monitor.
25 This senior researcher is not related to the current project and is part of another
26 research discipline within the department. At various moments in the study (not known
27 to the researcher in front) an appointment will be made with the researcher and
28 projectleader of the current project to monitor the study by making use of the checklist
29 of the department of general practice.
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33 **Adverse events**
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35 All (serious) adverse events and suspected unexpected serious adverse reactions
36 reported spontaneously by the subject or observed by the investigator or the staff will be
37 recorded.
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40 **Discussion**
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42 This will be the first study to investigate the effectiveness of treatment with TCS class I
43 vs class III on long-term control over 6-months follow-up of children in primary care with
44 AD.
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47 We chose an observational cohort design with an embedded pragmatic randomized
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open-label trial, as it might be difficult to randomize children in primary care at the moment they present with a flare-up. The observational cohort gives the opportunity to follow the course of AD in children in primary care with regard to the frequency and determinants of flare-ups, and the burden of disease. As primary outcome, we chose a clinical outcome relevant to patients. In AD, the appearance of the skin does not always closely reflect the subjective symptoms, i.e. when the latter causes a major impact on the child and family. (10, 11) Therefore, it was particularly important to design a trial with a validated participant-reported primary outcome.

A limitation of the study is the open-label design. Since participants know which treatment arm they will be assigned to, they cannot be blinded to the intervention. Also, because the GP must be able to adjust the treatment strategy or refer the child if required, the GP cannot be blinded. The research assistants will also be aware of the medication use of the child, as they have to register and weigh the medication.

Given that our primary outcome is patient-reported, the additional costs for blinding researchers to collect the objective data (i.e. EASI) did not seem justifiable.

Concerns have been reported about the safety of TCS application in children with regard to incorrect application. (26) Potential local side-effects of TCS are painful application, telangiectasia, atrophy, hypopigmentation, and striae. However, there is a lack of evidence from good quality research concerning these local side-effects of TCS. (27) Nevertheless, in a study on children with AD with a follow-up of 18 weeks, no difference was found in skin atrophy in children using class-III TCS for 3 days per week vs children using class I TCS. (16) Potential systemic effects of TCS may include suppression of the HPA axis, and osteoporosis, glaucoma, cataract, and growth reduction. Although there is lack of evidence about these potential systemic side-effects, it is reported that topical TCS has little to no effect on the HPA axis, osteoporosis and growth reduction. (1, 14, 15, 28) In addition, the treatment scheme for the class III TCS is within the recommended dosage of the Dutch guideline on AD. (1) Additionally, we chose fluticasone propionate 0.05% or 0.005% since it has a relatively short half-life as compared to the class III TCS that is recommended by the Dutch guideline (i.e. betamethasone). (1) In this way, we aim to further reduce the already low

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3 risk of potential (systemic) side-effects; therefore, we believe that it is safe to use a
4 class III TCS according to the previously described treatment scheme.
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7 Experience from dermatologists indicate that starting with a high-dose TCS leads to a
8 faster and better result as compared to starting with a low-dose TCS. However, most
9 children with AD are treated by a GP (only about 1% is referred to secondary care) and
10 have a milder form of AD as compared to patients treated by a dermatologist. (3)
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12 Whether the effects of initial treatment with a potent TCS as experienced in a specialist
13 setting can be transferred to treatment in primary care is unknown. Since the present
14 study will focus on these gaps, it will hopefully make an important contribution to
15 knowledge with respect to the use of local corticosteroids in children with AD treated in
16 general practice.
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22 Figures legends 23 24 25

26 Figure 1: GP= General practitioner, EASI= Eczema Area and Severity Index, POEM= Patient-Oriented Eczema Measure, AD= atopic dermatitis, TCS= Topical corticosteroid, PGA= Patient global assessment
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32 Table 1: POEM= Patient-Oriented Eczema Measure, EASI= Eczema Area and Severity Index, IDQOL= Infants' Dermatitis Quality of Life Index , CDLQI= Children's Dermatology Life Quality Index ,TCS= Topical corticosteroid, PGA= Patient global assessment, IGA= Investigator global assessment,
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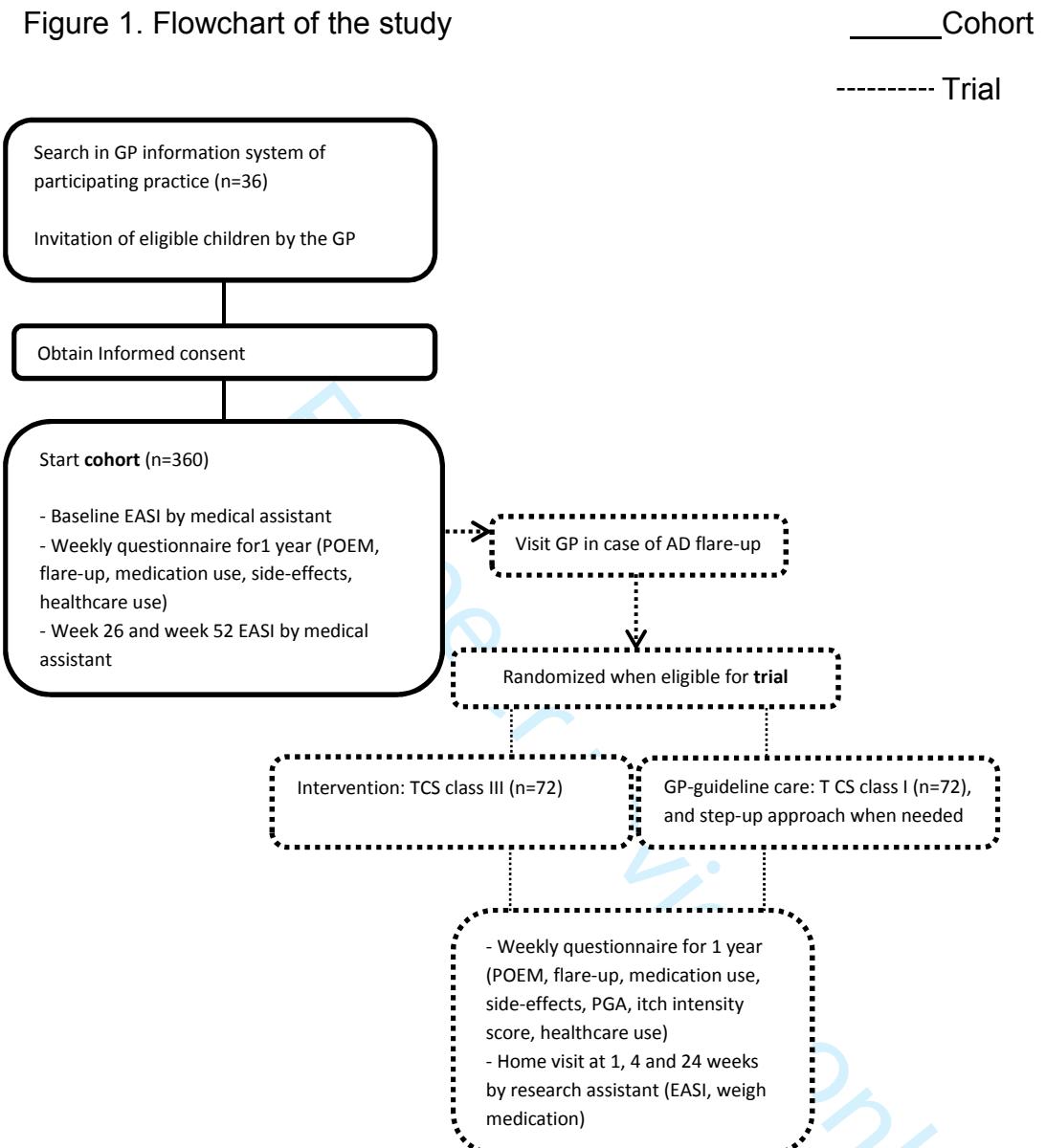
38 Figure 2: PIF=Patient information file
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REFERENCES

1. Dirven-Meijer PC DKC, Nonneman MGM, Van Sleeuwen D, De Witt-de Jong AWF, Burgers JS, Opstelten W, De Vries CJH. NHG-Standaard Eczeem. *Huisarts wet* 2014;57(5):240-252.
2. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics* 2008;122(4):812-824.
3. JCC Braspenning FS, RPTM Grol (redactie). Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Kwaliteit huisartsenzorg belicht. Utrecht/Nijmegen: NIVEL/WOK; 2004.
4. Watson W, Kapur S. Atopic dermatitis. *Allergy Asthma Clin Immunol* 2011;7 Suppl 1:S4.
5. Larsen FS, Hanifin JM. Epidemiology of atopic dermatitis. *Immunology and Allergy Clinics of North America* 2002;22(1):1-24.
6. Pols DHJ, Nielsen MMJ, Korevaar JC, Bindels PJE, Bohnen AM. Reliably estimating prevalences of atopic children: an epidemiological study in an extensive and representative primary care database. *NPJ Prim Care Respir Med* 2017;27(1):23.
7. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358(14):1483-1494.
8. Tollefson MM, Bruckner AL, Section On D. Atopic dermatitis: skin-directed management. *Pediatrics* 2014;134(6):e1735-1744.
9. Chang YS, Chou YT, Lee JH, Lee PL, Dai YS, Sun C, et al. Atopic dermatitis, melatonin, and sleep disturbance. *Pediatrics* 2014;134(2):e397-405.
10. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 1997;76(2):159-162.
11. Barbeau M, Bpharm HL. Burden of Atopic dermatitis in Canada. *Int J Dermatol* 2006;45(1):31-36.
12. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000;4(37):1-191.
13. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. *BMC Pediatr* 2016;16:75.
14. van Velsen SG, Knol MJ, van Eijk RL, de Vroede MA, de Wit TC, Lam MG, et al. Bone mineral density in children with moderate to severe atopic dermatitis. *J Am Acad Dermatol* 2010;63(5):824-831.
15. Thomas MW, Panter AT, Morrell DS. Corticosteroids' effect on the height of atopic dermatitis patients: a controlled questionnaire study. *Pediatr Dermatol* 2009;26(5):524-528.
16. Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S, et al. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. *Bmj* 2002;324(7340):768.
17. Kirkup ME, Birchall NM, Weinberg EG, Helm K, Kennedy CT. Acute and maintenance treatment of atopic dermatitis in children - two comparative studies with fluticasone propionate (0.05%) cream. *J Dermatolog Treat* 2003;14(3):141-148.
18. Vernon HJ, Lane AT, Weston W. Comparison of mometasone furoate 0.1% cream and hydrocortisone 1.0% cream in the treatment of childhood atopic dermatitis. *J Am Acad Dermatol* 1991;24(4):603-607.
19. Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care. Edinburgh: SIGN; 2011. (SIGN publication no125). [March 2011]. Available from URL: <http://www.sign.ac.uk>.
20. Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. *Br J Dermatol* 2017;176(4):979-984.

- 1
2
3 21. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome
4 Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin
5 Immunol* 2014;134(4):800-807.
6
7 22. Salek MS, Jung S, Brincat-Ruffini LA, MacFarlane L, Lewis-Jones MS, Basra MK, et al. Clinical
8 experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-
9 2012. *Br J Dermatol* 2013;169(4):734-759.
10
11 23. Basra MK, Gada V, Ungaro S, Finlay AY, Salek SM. Infants' Dermatitis Quality of Life Index: a
12 decade of experience of validation and clinical application. *Br J Dermatol* 2013;169(4):760-768.
13
14 24. Gaunt DM, Metcalfe C, Ridd M. The Patient-Oriented Eczema Measure in young children:
15 responsiveness and minimal clinically important difference. *Allergy* 2016;71(11):1620-1625.
16
17 25. Groenwold RH, Donders AR, Roes KC, Harrell FE, Jr., Moons KG. Dealing with missing outcome
18 data in randomized trials and observational studies. *Am J Epidemiol* 2012;175(3):210-217.
19
20 26. Aubert-Wastiaux H, Moret L, Le Rhun A, Fontenoy AM, Nguyen JM, Leux C, et al. Topical
21 corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. *Br J Dermatol*
22 2011;165(4):808-814.
23
24 27. Callen J, Chamlin S, Eichenfield LF, Ellis C, Girardi M, Goldfarb M, et al. A systematic review of
25 the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007;156(2):203-221.
26
27 28. Friedlander SF, Hebert AA, Allen DB, Fluticasone Pediatrics Safety Study G. Safety of fluticasone
28 propionate cream 0.05% for the treatment of severe and extensive atopic dermatitis in children as
29 young as 3 months. *J Am Acad Dermatol* 2002;46(3):387-393.
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Figure 1. Flowchart of the study



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| 7 Outcomes collected | Cohort | | | | Trial | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|---------|-----------------------------------------------------|-----------------------------------------------------|--------|--------|---------|-----------------------------------------------------|
| | Baseline | Week 26 | Week 52 | Weekly for 52 weeks | Baseline | Week 1 | Week 4 | Week 24 | Weekly for 24 weeks |
| 12 Proxy-reported/patient-reported outcomes <ul style="list-style-type: none"> 13 • Eczema severity over past week (POEM) 14 • Eczema-related quality of life (IDQOL/CDLQI) 15 • Flare up 16 • Amount of days emollients used in past week 17 • Itch intensity score 18 • Patient global assessment 19 • Amount of days TCS used in past week 20 • Use of medication other than TCS in past week 21 • Adverse effects from treatment in past week 22 • Physician visits in past week | V V | V | V | V V V V V V V V V V V | V | V | V | V | V V V V V V V V V V V |
| 31 Objective-reported outcomes <ul style="list-style-type: none"> 32 • Three-Item Severity score 33 • Eczema area and severity index (EASI) 34 • Investigator global assessment 35 • Weight 36 • Height 37 • Head circumference 38 • Weigh medication | V | V | V | | V V V V V V V V V V V | V | V | V | V V V V V V V V V V V |

For peer review only



Informatiebrief voor ouders/verzorgers over het onderzoek naar de behandeling van eczeem bij kinderen, de Rotterdam Eczeemstudie.

Effectiviteit van verschillende sterktes lokale corticosteroïden: bewijs leveren voor een betere behandelstrategie voor kinderen met eczeem in huisartsenpraktijk.

Geachte ouders/verzorgers,

Van uw huisarts heeft u een brief ontvangen waarin u werd gevraagd uw kind mee te laten doen aan een onderzoek, de Rotterdam Eczeemstudie. Meedoelen is vrijwillig.

U heeft de antwoordkaart teruggestuurd en aangegeven eventueel interesse te hebben om mee te doen. Aan u is ook al verteld wat het onderzoek inhoudt. U kunt de informatie in deze brief terugvinden. U beslist zelf of u wilt dat uw kind meedoet. Om mee te doen is wel schriftelijke toestemming nodig van beide ouders of de voogd.

Voordat u beslist of u wilt meedoelen aan dit onderzoek, krijgt u uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door. Bespreek het met uw kind, partner, vrienden of familie. Ook is er een onafhankelijk persoon die veel weet van het onderzoek. Lees ook de Algemene brochure 'Medisch-wetenschappelijk onderzoek,' daar staat veel algemene informatie over medisch-wetenschappelijk onderzoek in. Heeft u na het lezen van de informatie nog vragen? Dan kunt u terecht bij de onderzoeker. In bijlage B vindt u haar contactgegevens.

1. Algemene informatie

Dit onderzoek wordt gedaan door de afdeling Huisartsgeneeskunde van het Erasmus Medisch Centrum (Erasmus MC). De medisch ethische toetsingscommissie van het Erasmus MC heeft dit onderzoek goedgekeurd.

Wat is eczeem?

Uw kind heeft eczeem. Eczeem is een jeukende huiduitslag met roodheid, zwelling, schilfers, bultjes, blaasjes, kloofjes of korstjes. De huid is meestal droog. Vaak zie je ook beschadigingen van de huid door het krabben. Eczeem begint vaak al op jonge leeftijd, soms al 3 tot 4 maanden na de geboorte, maar het kan ook pas op latere leeftijd ontstaan. De klachten kunnen gedurende perioden verergeren en weer verdwijnen. Als de klachten verergeren noemen wij dat een opvlamming. Er is geen behandeling om eczeem te genezen, wel zijn er medicijnen om de klachten van eczeem te verminderen.

2. Wat is het doel van het onderzoek?

Met dit onderzoek willen wij kijken hoeveel last kinderen hebben van eczeem en hoe we eczeem het beste kunnen behandelen. Omdat eczeem een heel wisselend beloop heeft, willen we de ernst en klachten van het eczeem bekijken gedurende één jaar. Dit noemen we het observatiegedeelte van het onderzoek.

Er bestaan verschillende soorten medicatie om de klachten van eczeem te behandelen. Vaak gaat het om een neutrale vette zalf en corticosteroïdencrème of -zalf die men op de huid

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smeert. Dit laatste wordt ook wel hormooncrème genoemd. Deze crèmes worden vaak gebruikt bij een opvlamming van eczeem. De corticosteroïdcrèmes zijn in vier klassen ingedeeld, deze staan voor de sterkte van de zalf. Hoe hoger de klasse, hoe sterker het medicijn is. Door het gebruik van deze medicijnen kunnen de klachten van eczeem afnemen binnen enkele dagen tot weken. In dit onderzoek kijken we welke corticosteroïdcrème (mild of sterk) beter werkt voor de klachten van het eczeem op de korte en op de lange termijn. Hiervoor kijken wij naar de ernst van het eczeem over een periode van 6 maanden. Dit noemen we het interventiedeel van het onderzoek.

Uiteindelijk kunnen we met de uitkomst van dit onderzoek beter inzicht krijgen in het verloop en de ernst van eczeem en ervoor zorgen dat kinderen en jongeren met eczeem een betere behandeling krijgen.

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3. Welke medicijnen worden er gebruikt in dit onderzoek?

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Er zijn drie soorten medicijnen (crèmes) die we in dit onderzoek zullen gebruiken. Alle drie de crèmes bevatten corticosteroïden en worden gebruikt voor de behandeling van een opvlamming van eczeem. Corticosteroïden zijn afgeleid van het bijnierschorshormoon. Corticosteroïden remmen de ontstekingsreactie in de huid en helpen goed tegen de jeuk. In dit onderzoek wordt gebruik gemaakt van een klasse I (mild: hydrocortisonacetaatcrème 1%), klasse II (matig: triamcinolonacetoneidecrème 0.1%) en klasse III crème (sterk: fluticasonepropionatecrème 0.05%).

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4. Hoe wordt het onderzoek uitgevoerd?

In dit onderzoek doen ruim 350 kinderen mee van 1 tot 18 jaar in zuidwest Nederland. Als u meedoet, duurt dat in totaal 6 tot 18 maanden voor u en uw kind. In bijlage A hebben wij een schematisch overzicht van het onderzoek toegevoegd. Binnenkort zullen wij u bellen en kunnen wij vragen beantwoorden die u heeft na het lezen van deze informatiebrief.

Observatiedeel: Als u instemt met deelname aan het onderzoek volgt een afspraak bij de huisarts (in opleiding) in uw eigen huisartsenpraktijk en behoort uw kind eerst tot het observatiedeel van het onderzoek. Tijdens de observatieperiode vragen we u of uw kind wekelijks een korte online vragenlijst in te vullen. Hierin kan u of uw kind aangeven welke klachten hij of zij de afgelopen week heeft gehad. Het invullen zal iedere week max 5 minuten duren. Mocht het nodig zijn, dan kunt u uw kind helpen met het invullen van de online vragenlijst.

Naast de wekelijkse vragenlijst vragen we u om 6 en 12 maanden na het starten van het onderzoek langs de huisarts (in opleiding) te gaan om de ernst van het eczeem vast te laten leggen en een vragenlijst in te vullen, dit duurt ongeveer 15 minuten. Na de laatste afspraak bij de huisarts (in opleiding), die zal plaatsvinden 12 maanden na de eerste afspraak, is het observatiedeel afgelopen.

Interventiedeel: Mocht uw kind tijdens het jaar last krijgen van een verergering van het eczeem, een opvlamming, dan neemt u contact op met de huisarts. Deze zal, als uw kind

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extra medicatie nodig heeft, via ons te horen krijgen welk middel uw kind voorgeschreven krijgt om de opvlamming te behandelen. Om de verdeling zo eerlijk mogelijk te houden, wordt de verdeling bepaald door loting. Uw kind doet vanaf dat moment mee aan het interventiedeel van het onderzoek. Voor het interventiedeel krijgt een groep corticosteroïdcrème klasse I (dit is de standaardbehandeling van de huisarts bij een opvlamming) en de andere groep krijgt de corticosteroïdcrème klasse III voorgeschreven. Beide groepen krijgen ook het advies om neutrale vette zalf tegen de opvlamming te gebruiken.

Tijdens de behandeling van de opvlamming van het eczeem vragen we u of uw kind wekelijks een online vragenlijst in te vullen, tot 24 weken na de start van de behandeling. Hierin kan u of uw kind aangeven welke klachten hij of zij de afgelopen week heeft gehad. Het invullen zal iedere week max 5 minuten duren. Mocht het nodig zijn, dan kunt u uw kind helpen met het invullen van de online vragenlijst.

Als uw kind in de groep zit die start met de corticosteroïd klasse I en het blijkt dat deze niet voldoende werkt, dan zal uw kind in overleg met de huisarts overstappen op het gebruik van een klasse II, triamcinolonacetonidecrème. Is uw kind jonger dan 2 jaar en zit hij of zij in de groep die start met de corticosteroïd klasse III crème dan zal na het verbeteren van de klachten overgestapt worden op klasse II, de triamcinolonacetonidecrème.

Bij alle groepen zal na het verbeteren van de klachten het smeren van de corticosteroïd crème afgebouwd worden volgens een afbouwschema.

Na 1 week, na 4 weken en na 24 weken na het starten van de behandeling komt de onderzoeksassistent bij u thuis langs om de ernst van het eczeem vast te leggen, een vragenlijst af te nemen en de medicatie te wegen, hiermee kunnen de onderzoekers precies bepalen hoeveel corticosteroïdcrème gebruikt wordt. Tijdens de huisbezoeken meet de onderzoeksassistent ook lengte, gewicht, buikomtrek en hoofdomtrek. Deze metingen doen wij om te kijken naar bijwerkingen die eventueel op kunnen treden.

Na het laatste bezoek van de onderzoeksassistent, 24 weken na starten van de behandeling, is het onderzoek klaar.

U kunt ervoor kiezen om alleen mee te doen met het observatiedeel van het onderzoek. U kunt dit aangeven op de toestemmingsverklaring, zie bijlage E.

5. Wat wordt er van uw zoon of dochter verwacht?

Als uw kind deelneemt aan het observatiedeel van het onderzoek, vragen wij u of uw kind wekelijks een online vragenlijst in te vullen over de ernst van het eczeem in de afgelopen week. Daarnaast vragen wij u om na 26 weken en na 52 weken een bezoek te brengen aan de huisarts in opleiding, deze zal twee vragenlijsten afnemen.

Als uw kind deelneemt aan het interventiedeel van het onderzoek, vragen wij uw kind gebruik te maken van de toegewezen medicatie. Deze medicatie zal bij het starten eenmaal daags gebruikt worden. Zijn de klachten van het eczeem verminderd, dan kunt u volgens het afbouwschema gaan afbouwen met het smeren van de corticosteroïdcrème. Naast de medicatie vragen wij u of uw kind eenmaal per week een online vragenlijst in te vullen.

6. Welke bijwerkingen kan uw zoon of dochter verwachten?

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3 Alle drie de gebruikte middelen zijn bekende middelen die al jaren op de markt zijn en
4 gebruikt worden voor onder andere de behandeling van eczeem. De bijwerkingen van deze
5 medicijnen zijn daarom goed bekend. De meest voorkomende bijwerkingen van
6 corticosteroïdcrème zijn een dunne huid, kleine zichtbare bloedvaatjes, streperigheid van de
7 huid (ook wel striae genoemd) en niet-wegdrukbare roodheid. Andere, minder vaak
8 voorkomende bijwerkingen van de corticosteroïdcrèmes staan in bijlage D en in de bijsluiter.
9 Als uw kind ernstige bijwerkingen krijgt die niet beschreven staan in de bijlage en bijsluiter
10 moet u direct contact opnemen met uw huisarts. De bijwerkingen die uw kind heeft, moeten
11 worden ingevuld in de wekelijkse online vragenlijst.
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1617 **7. Wat zijn voor mijn zoon/dochter de nadelen?**
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1920 Uw kind zal geen medicatie mogen gebruiken uit de andere groep dan ingedeeld, zonder
21 eerst te overleggen met de huisarts. Daarnaast vragen wij u of uw kind wekelijks een korte
22 online vragenlijst in te vullen.23 Zoals elk geneesmiddel kunnen de geneesmiddelen die gebruikt worden in deze studie
24 bijwerkingen veroorzaken, maar niet iedereen krijgt hiermee te maken.25 Verder moet nog gemeld worden dat de medicatie niet gebruikt mag worden tijdens de
26 zwangerschap. Het is dus heel belangrijk dat uw dochter niet zwanger is of wordt als zij mee
27 gaat doen aan het onderzoek. Mocht uw dochter zwanger zijn, geef dit dan door aan de
28 onderzoekers. Wij vragen haar dan te stoppen met het onderzoek.
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3132 **8. Wat gebeurt er bij verzet van uw zoon of dochter bij deelname aan het
33 onderzoek?**
3435 Het kan zijn dat uw zoon of dochter tijdens het onderzoek op de praktijk of de huisbezoeken
36 zich verzet, denk hierbij aan sterke angst, verdriet of boosheid. De onderzoeker moet het
37 onderzoek dan direct stoppen.
38
3940 **9. Kan ik mijn zoon/dochter tijdens het onderzoek nog terugtrekken?**
4142 Ja, de deelname van uw kind is volkomen vrijwillig. Hij of zij mag op ieder moment, zonder
43 opgaaf van reden, stoppen met het onderzoek. Dit heeft geen enkel gevolg voor zijn of haar
44 verdere behandeling. Meer informatie hierover vindt u in de Algemene Brochure.
45
4647 **10. Vergoeding voor mee doen**
4849 De studieduur en behandeling van de huisarts voor het onderzoek kost u niets. U wordt
50 niet betaald voor het meedoen aan dit onderzoek. Verder krijgt u een vergoeding voor uw
51 (extra) reiskosten. Daarnaast krijgt uw kind na afronden van het onderzoek een kleinigheidje.
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11. Wat gebeurt er als het onderzoek is afgelopen?

Als het onderzoek is afgelopen komen de onderzoekers de overgebleven medicatie en (eventuele) lege medicijntubes ophalen. Bewaar daarom de medicatie en verpakkingen goed, ook als ze leeg zijn. Als dank voor uw deelname krijgt uw kind een klein bedankje van ons. Als uw kind de medicatie nog na de onderzoeksperiode wilt blijven gebruiken, kunt u een recept bij de huisarts vragen. Het is mogelijk dat u, uw kind of de onderzoekers het onderzoek tussentijds willen stoppen. Als de onderzoekers tussentijds willen stoppen met het onderzoek, zal u hier duidelijk over bericht worden

12. Is uw kind verzekerd wanneer hij/zij aan het onderzoek meedoet?

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt de schade als gevolg van het onderzoek. Dit geldt voor schade die naar boven komt tijdens het onderzoek, of binnen vier jaar na het einde van het onderzoek. In bijlage C vindt u de verzekerde bedragen, de uitzonderingen en de adresgegevens van de verzekeraar.

13. Wordt u geïnformeerd als er tussentijds voor u relevante informatie over de studie bekend wordt?

Als er tussentijdse informatie bekend wordt die van invloed kan zijn op de toestemming van uw zoon of dochter, dan zult u daarvan tijdig op de hoogte worden gesteld.

14. Wat gebeurt er met de onderzoeksgegevens van mijn zoon of dochter?

Onderzoeksgegevens kunnen slechts door daartoe geautoriseerde en gekwalificeerde medewerkers van het onderzoeksteam, medewerkers van de Inspectie voor de Gezondheidszorg en leden van de Medisch Ethische Toetsingscommissie van het Erasmus MC Rotterdam worden ingezien. Dit is om te controleren of het onderzoek goed en betrouwbaar is uitgevoerd. Onderzoeksgegevens zullen worden gehanteerd met inachtneming van de Wet bescherming persoonsgegevens en het privacyreglement van het Erasmus MC Rotterdam. Dit wil zeggen dat de persoonsgegevens die tijdens het onderzoek worden verzameld, vervangen worden door een codenummer. Alleen dit nummer zal gebruikt worden voor studiedocumentatie, rapporten of publicaties van dit onderzoek. Alleen de verantwoordelijk onderzoeker weet wie de persoon achter het codenummer is. De gegevens worden gedurende 15 jaar bewaard.

15. Wordt de huisarts van uw zoon of dochter geïnformeerd bij deelname?

De werving voor dit onderzoek is via de huisarts gegaan, daarnaast zal de eerste afspraak voor het onderzoek plaatsvinden bij de huisarts (in opleiding). De huisarts is dus op de hoogte van deelname aan het onderzoek.



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4 **16. Welke medisch-ethische toestemmingscommissie heeft dit**
5 **onderzoek goedgekeurd?**6
7 De Medisch Ethische Toetsingscommissie van het Erasmus MC Rotterdam heeft dit
8 onderzoek goedgekeurd. Meer informatie over de goedkeuring vindt u in de Algemene
9 Brochure.
10
1112 **17. Ondertekening toestemmingsformulier**
1314 Wanneer u voldoende bedenktijd heeft gehad, wordt u gevraagd te beslissen over deelname
15 aan dit onderzoek. Indien u toestemming geeft, zullen wij u vragen deze op de bijbehorende
16 toestemmingsverklaring schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u
17 aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek.
1819 Het handtekeningenblad wordt door uw behandelend arts bewaard. U krijgt een kopie of een
20 tweede exemplaar van deze toestemmingsverklaring.
2122 Als uw kind jonger is dan 16 jaar, ondertekenen de ouders die het gezag uitoefenen of de
23 voogd dit formulier. Kinderen van 12 tot en met 15 jaar moeten daarnaast zelf een formulier
24 ondertekenen.
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2627 Dank voor uw aandacht.
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5 De Rotterdam Eczeemstudie

6 Proefpersoneninformatie

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16. Bijlagen bij deze informatie

- A. Schematisch overzicht onderzoek
- B. Contactgegevens
- C. Informatie over de verzekering
- D. Informatie over bijwerkingen medicatie
- E. Toestemmingsverklaring ouders/verzorgers
- F. Algemene brochure medisch-wetenschappelijk onderzoek met mensen

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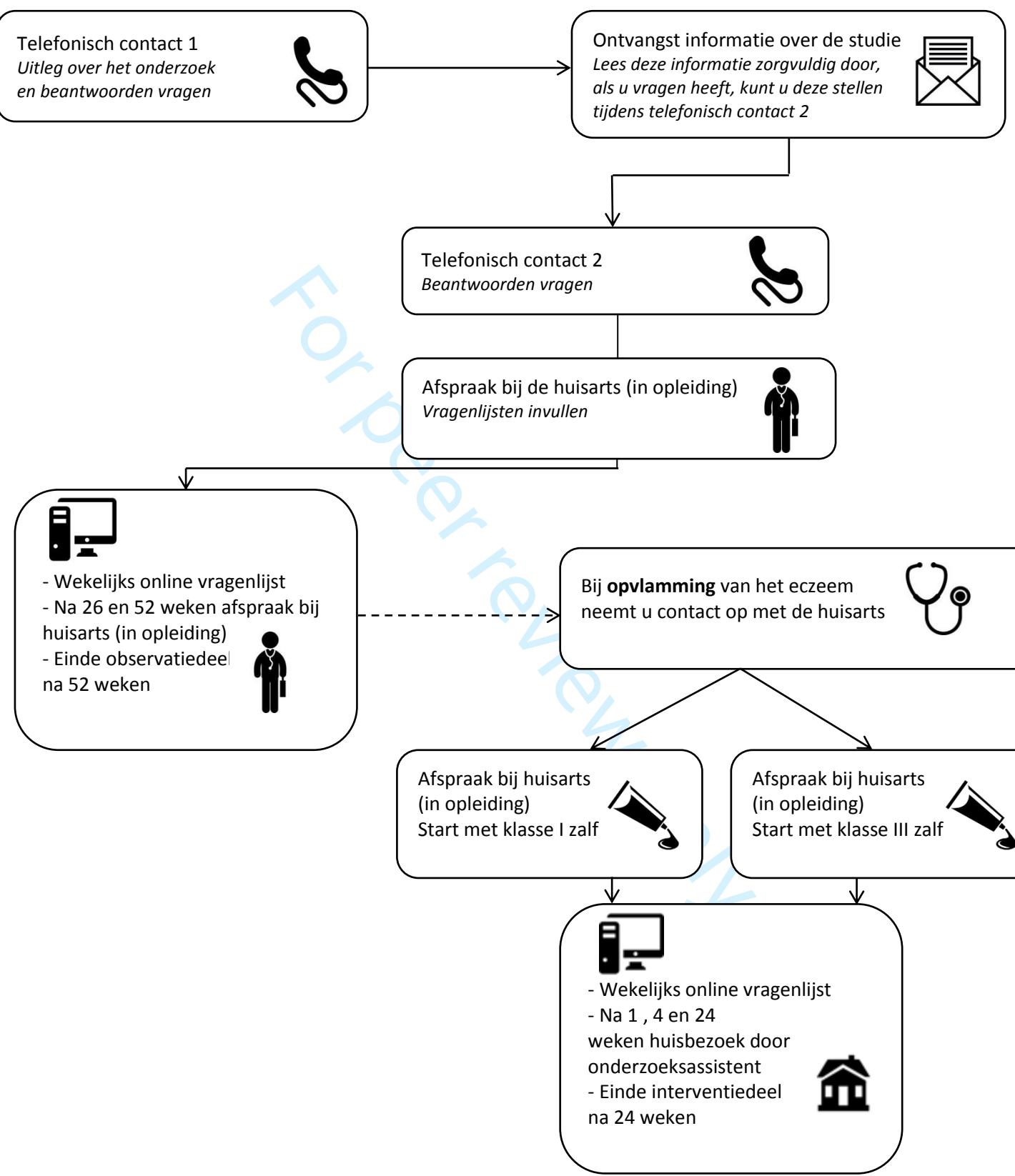
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Bijlage A: Schematisch overzicht onderzoek



1 De Rotterdam Eczeemstudie
2 Proefpersoneninformatie3 **Bijlage B: Contactgegevens**
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U kunt voor verdere informatie over het onderzoek of over de te gebruiken medicatie terecht bij:

9 Mevrouw K.F. van Halewijn, onderzoeker
10 Afdeling Huisartsgeneeskunde Rotterdam
11 E-mail: k.vanhalewijn@erasmusmc.nl
12 Tel: 010-7032117
13
14
1516 Ook uw huisarts is op de hoogte van dit onderzoek, als u vragen heeft, kunt u die ook aan
17 hem of haar stellen.
1819 Als u twijfelt over deelname kunt u een onafhankelijk arts raadplegen die zelf niet bij het
20 onderzoek betrokken is, maar wel deskundig is op het gebied van dit onderzoek. Ook als u
21 voor of tijdens het onderzoek vragen hebt die u liever niet aan de onderzoekers stelt, kunt u
22 contact opnemen met de onafhankelijk arts:
23
2425 Mevrouw A. Verwoerd, huisarts. Telefoonnummer: 010-7044194
26
2728 Als u niet tevreden bent over het onderzoek of de behandeling kunt u terecht bij de
29 onafhankelijke klachtencommissie van het Erasmus MC. De klachtencommissie is te
30 bereiken onder telefoonnummer 010-4633198.
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Bijlage C: informatie over de verzekering

Voor iedereen die meedoet aan dit onderzoek, heeft het Erasmus MC een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde ervan. Schade moet u binnen die vier jaar aan de verzekeraar hebben gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt.

Deze bepalingen staan in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Dit besluit staat op www.ccmo.nl, de website van de Centrale Commissie Mensgebonden Onderzoek (zie ‘Bibliotheek’ en dan ‘Wet- en regelgeving’).

Bij schade kunt u direct contact leggen met de verzekeraar via e-mail of telefoon, zie onderstaande contact gegevens..

De verzekeraar van het onderzoek is:

Naam: CNA Insurance Company Limited
Adres: Strawinskylaan 703, 1077 XX Amsterdam
Telefoonnummer: 020 - 573 72 74
E-mail: esther.vanherk@cnahardy.com
Contactpersoon: Esther van Herk

De verzekering biedt een dekking van € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek (en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever).

De verzekering dekt de volgende schade niet:

- schade door een risico waarover u in de schriftelijke informatie bent ingelicht. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
 - schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan;
 - schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
 - schade aan uw nakomelingen, als gevolg van een negatief effect van het onderzoek op u of uw nakomelingen;
 - schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.



Bijlage D: Informatie over de bijwerkingen van de medicatie

Hydrocortisonacetaatcrème 1% (klasse I)

Zoals elk geneesmiddel kan hydrocortisonacetaatcrème 1% bijwerkingen veroorzaken, al krijgt niet iedereen daarmee te maken.

Bijwerkingen kunnen

- zeer vaak voorkomen: *bij meer dan 1 op de 10 patiënten*
- vaak voorkomen: *bij minder dan 1 op de 10, maar bij meer dan 1 op de 100 patiënten*
- soms voorkomen: *bij minder dan 1 op de 100, maar bij meer dan 1 op de 1.000 patiënten*
- zelden voorkomen: *bij minder dan 1 op de 1.000, maar bij meer dan 1 op de 10.000 patiënten*
- zeer zelden voorkomen: *bij minder dan 1 op de 10.000 patiënten, inclusief incidentele meldingen*

Bijwerkingen die **vaak** voorkomen:

- huidatrofie, dikwijls blijvend, met dunner worden van de huid
- huidstriemen (striae atrophicae)
- roodheid (rosacea-achtig) en blaarvorming en/of schilfering van de huid rondom de mond, met of zonder huidatrofie (striae atrophicae)
- versterkt terugkeren van de klachten na stoppen met het gebruik van de crème (rebound-effect), wat kan leiden tot afhankelijkheid van steroïden
- vertraging van het genezingsproces
- bleek worden van de huid (depigmentatie)
- verwijding van bloedvaatjes vlak onder het oppervlak van de huid (teleangiëctasieën), neiging tot bloeden.

Bijwerkingen die **soms** voorkomen:

- verergeren van psoriasis (terugkerende huidaandoening gepaard gaande met schilferende, droge huiduitslag) in psoriasis pustularis (psoriasis gepaard gaande met de vorming van puisten)
- het niet tijdig opmerken of verergeren van parasitaire, schimmel- en bacteriële infecties.

Bijwerkingen die **zelden** komen voor:

- overgevoeligheidsreacties (roodheid, jeuk);
- effecten op het oog, zoals verhoogde oogdruk
- overmatige haargroei (hyperichtosis)
- geelwitte knopgrootte knobbeltjes (colloïd-milia)
- bruinrode huidknobbeltjes (granuloma gluteale)

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1011 **Bijwerkingen op de rest van het lichaam:**12 Bijwerkingen op de rest van het lichaam (systemische bijwerkingen) ten gevolge van gebruik
13 van corticosteroïdpreparaten komen zelden voor, maar kunnen ernstig zijn.
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1617 Remming van de bijnierschors kan vooral van betekenis zijn bij langdurig gebruik.
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1920 De kans op bijwerkingen op de rest van het lichaam is het grootst bij:
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- 23 • toepassing waarbij de huid wordt afgesloten (afsluitend verband, plastic, huidplooien)
-
- 24 • toepassing op grote huidoppervlakken
-
- 25 • langdurige toepassing
-
- 26 • het gezicht, de behaarde huid en de huid van de geslachtsdelen zijn bijzonder
-
- 27 gevoelig voor lokale effecten.
-
- 28 • toepassing bij kinderen (de dunne huid en het relatief grote huidoppervlak maken
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- 29 kinderen zeer gevoelig).
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50 **Heeft uw kind veel last van een bijwerking? Of heeft uw kind een bijwerking die hier
51 niet bij staat? Neem dan contact op met uw huisarts.**
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89 **Triamcinolonacetonidecrème 0.1% (klasse II)**
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1112 Zoals elk geneesmiddel kan triamcinolonacetonidecrème 0.1% bijwerkingen veroorzaken, al
13 krijgt niet iedereen daarmee te maken.
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1516 *Bijwerkingen kunnen*
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- 19 - zeer vaak voorkomen:
- bij meer dan 1 op de 10 patiënten*
-
- 20 - vaak voorkomen:
- bij minder dan 1 op de 10, maar bij meer dan 1 op de 100 patiënten*
-
- 21 - soms voorkomen:
- bij minder dan 1 op de 100, maar bij meer dan 1 op de 1.000 patiënten*
-
- 22 - zelden voorkomen:
- bij minder dan 1 op de 1.000, maar bij meer dan 1 op de 10.000*
-
- 23 patiënten
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- 24 - zeer zelden voorkomen:
- bij minder dan 1 op de 10.000 patiënten, inclusief incidentele*
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- 25
- meldingen*
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28 *Bijwerkingen die vaak voorkomen:*
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- 31 • huidatrofie, dikwijls blijvend, met dunner worden van de huid
-
- 32 • huidstriemen (striae atrophicae)
-
- 33 • roodheid (rosaceaachtige) en blaarvorming en/of schilfering van de huid rondom de
-
- 34 mond, met of zonder huidatrofie
-
- 35 • versterkt terugkeren van de klachten na stoppen met het gebruik van de crème
-
- 36 (rebound-effect), wat kan leiden tot afhankelijkheid van steroïden
-
- 37 • vertraging van het genezingsproces
-
- 38 • bleek worden van de huid (depigmentatie)
-
- 39 • verwijding van bloedvaatjes vlak onder het oppervlak van de huid
-
- 40 (teleangiëctastieën), neiging tot bloeden.
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43 *Bijwerkingen die soms voorkomen:*
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- 46 • verergeren van psoriasis (terugkerende huidaandoening gepaard gaande met
-
- 47 schilferende, droge huiduitslag) in psoriasis pustularis (psoriasis gepaard gaande
-
- 48 met de vorming van puisten)
-
- 49 • het niet tijdig opmerken of verergeren van parasitaire, schimmel- en bacteriële
-
- 50 infecties.
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53 *Bijwerkingen die zelden voorkomen:*
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- 56 • overmatige haargroei (hypertrichosis)
-
- 57 • geelwitte speldenknopgrote knobbeltjes (colloid-milia)
-
- 58 • rood worden en toenemende afschilfering van de huid (erythrosis interfollicularis colli)
-
- 59 • overgevoeligheidsreacties op de plaats van insmeren met roodheid van de huid en
-
- 60 jeuk (contactallergie)
-
- 61 • bruinrode huidknobbeltjes (granuloma gluteale).
-
- 62 • een verhoging van de oogboldruk en vergroting van de kans op grijze staar
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- 63 (cataract).
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1011 **Bijwerkingen op de rest van het lichaam:**12 Bijwerkingen op de rest van het lichaam (systemische bijwerkingen) ten gevolge van gebruik
13 van corticosteroïdpreparaten komen zelden voor, maar kunnen ernstig zijn.
14
1516 Remming van de bijnierschors kan vooral van betekenis zijn bij langdurig gebruik.
17
1819 De kans op bijwerkingen op de rest van het lichaam is het grootst bij:
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- 22
- 1 • toepassing waarbij de huid wordt afgesloten (afsluitend verband, plastic, huidplooien)
 - 2 • toepassing op grote huidoppervlakken
 - 3 • langdurige toepassing
 - 4 • het gezicht, de behaarde huid en de huid van de geslachtsdelen zijn bijzonder
5 gevoelig voor lokale effecten.
 - 6 • toepassing bij kinderen (de dunne huid en het relatief grote huidoppervlak maken
7 kinderen zeer gevoelig).
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Heeft uw kinds veel last van een bijwerking? Of heeft uw kind een bijwerking die hier niet bij staat? Neem dan contact op met uw huisarts.

De Rotterdam Eczeemstudie

Proefpersoneninformatie



Fluticasonepropionaatcrème 0.05% (klasse III)

Zoals elk geneesmiddel kan fluticasonpropionaatcrème 0.05% bijwerkingen veroorzaken, al krijgt niet iedereen daarmee te maken.

Bijwerkingen zullen zichtbaar zijn op de huid en kunnen andere delen van het lichaam betreffen, als er een grote hoeveelheid van het geneesmiddel door de huid is opgenomen en in het bloed terecht is gekomen.

Als de huidaandoening erger wordt, of als de huid gezwollen raakt tijdens de behandeling, kan het zijn dat uw kind allergisch is voor het geneesmiddel, dat uw kind een infectie heeft, of dat uw kind een andere behandeling moet krijgen. Stop dan met het gebruik van dit geneesmiddel en neem zo snel mogelijk contact op met uw huisarts.

Bijwerkingen kunnen

- zeer vaak voorkomen: bij meer dan 1 op de 10 patiënten
 - vaak voorkomen: bij minder dan 1 op de 10, maar bij meer dan 1 op de 100 patiënten
 - soms voorkomen: bij minder dan 1 op de 100, maar bij meer dan 1 op de 1.000 patiënten
 - zelden voorkomen: bij minder dan 1 op de 1.000, maar bij meer dan 1 op de 10.000 patiënten
 - zeer zelden voorkomen: bij minder dan 1 op de 10.000 patiënten, inclusief incidentele meldingen

Bijwerkingen die **vaak** voorkomen:

- jeukende huid (pruritus)

Bijwerkingen die **soms** voorkomen:

- lokaal branderig gevoel van de huid/zere huid

Bijwerkingen die kunnen optreden (frequentie niet bekend):

- allergische reactie op de plaats waar het middel is aangebracht
 - verergering (exacerbaties) van de huidproblemen
 - met puistjes gepaard gaande psoriasis (psoriasis pustularis)
 - roodheid van de huid (erytheem)
 - huiduitslag (rash)
 - netelroos of galbulen (urticaria)
 - infectie die kan optreden bij mensen met verminderde weerstand (opportunistische infectie)
 - dundere huid (atrofie)
 - streepvorming van de huid (striae)
 - ontkleuring van de huid (hypopigmentatie)
 - overmatige haargroei in bepaald gebied (hypertrichose)

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6 Bijwerkingen die kunnen optreden (frequentie niet bekend) bij langdurig gebruik van dit
7 geneesmiddel, of het gebruik onder een afsluitend verband:

- 8 • gewichtstoename/zwaarlijvigheid
-
- 9 • vollemaansgezicht, grote buikomvang (centrale obesitas), (syndroom van Cushing)
-
- 10 • dunner worden van de huid, dit kan leiden tot streepvormige littekens (striae)
-
- 11 • rimpeling van de huid
-
- 12 • droge huid
-
- 13 • het zichtbaar worden van bloedvaten onder het huidoppervlak (teleangiëctastieën)
-
- 14 • pigmentatieveranderingen
-
- 15 • overmatige haargroei (hypertrichose)
-
- 16 • haarverlies/gebrek aan haargroei (alopecia)/ haar dat er beschadigd uitziet
-
- 17 (trichorrhesis)
-
- 18 • vertraagde gewichtstoename
-
- 19 • langzame groei

20 Bijwerkingen die naar voren kunnen komen uit bloedtesten of als uw arts u onderzoekt
21 (frequentie niet bekend):

- 22 • verminderde waarden van in het lichaam voorkomend bijnierschorshormoon (cortisol)
-
- 23 • te hoog suikergehalte in het bloed (hyperglykemie)/glucose in de urine (glucosurie)
-
- 24 • verhoogde bloeddruk (hypertensie)
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- 25 • botontkalking (osteoporose)
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- 26 • grijze staar (cataract)
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- 27 • groene staar (glaucoom)

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37 **Heeft uw kind veel last van een bijwerking? Of heeft uw kind een bijwerking die hier
38 niet bij staat? Neem dan contact op met uw huisarts.**



Bijlage E: Toestemmingsverklaring voor ouders of voogd

Onderzoek naar de behandeling van eczeem bij kinderen, de Rotterdam Eczeemstudie

Ik ben gevraagd om toestemming te geven voor deelname van de volgende persoon/mijn kind aan dit medisch-wetenschappelijke onderzoek:

Naam proefpersoon (kind):

Geboortedatum: ___ / ___ / ___

- Ik heb de informatiebrief voor de ouders/verzorgers van de proefpersoon gelezen. Ik kon aanvullende vragen stellen. Deze vragen zijn naar tevredenheid beantwoord. Ik heb voldoende tijd gehad om te beslissen of mijn kind meedoet.
- Ik weet dat meedoen helemaal vrijwillig is. Ik weet dat ik op ieder moment kan beslissen dat mijn kind toch niet meedoet. Daarvoor hoeft ik geen reden te geven.
- Ik geef toestemming om de huisarts van mijn kind te vertellen dat hij/zij meedoet aan dit onderzoek.
- Ik geef toestemming voor het opvragen van informatie bij de over medische voorgeschiedenis en medicatiegebruik.
- Ik weet dat sommige mensen de gegevens van mijn kind kunnen zien. Die mensen staan vermeld in de Algemene brochure.
- Ik geef toestemming om de (medische) gegevens van mijn kind te gebruiken, voor de doelen die in de informatiebrief staan.
- Ik geef toestemming om de gegevens van mijn kind 15 jaar na afloop van dit onderzoek te bewaren.
- Ik geef wel/een* toestemming om mijn kind deel te laten nemen aan het interventiedeel van het onderzoek als hij/zij een opvlamping heeft van het eczeem, zoals te lezen is in de informatiebrief.
- Ik geef wel/een* toestemming om mij te benaderen voor vervolgonderzoek.
- Ik ga ermee akkoord dat mijn kind meedoet aan dit onderzoek

Naam ouder/voogd**:

Handtekening:

Datum: ___ / ___ / ___

Naam ouder/voogd**:

Handtekening:

Datum: ___ / ___ / ___

Ik verklaar hierbij dat ik bovengenoemde persoon/personen volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de ouder of voogd zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam onderzoeker:

Handtekening:

Datum: ___ / ___ / ___

* Doorhalen wat niet van toepassing is.

** Wanneer het kind jonger dan 16 jaar is, ondertekenen de ouders die het gezag uitoefenen of de voogd dit formulier. Kinderen van 12 t/m 15 jaar die zelfstandig beslissingen kunnen nemen (wilsbekwaam zijn), moeten daarnaast formulier "Toestemmingsverklaring voor jongeren 12 t/m 17 jaar" ondertekenen.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|-----------------------------------|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | 3 | Date and version identifier | footer |
| Funding | 4 | Sources and types of financial, material, and other support | 1 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |

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1
2 **Introduction**
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| | | | |
|--------------------------|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4 and 5 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 5 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, cluster, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 and 6 |

14
15 **Methods: Participants, interventions, and outcomes**
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| | | | |
|----------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | n/a |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 9 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variables (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8 and 9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | figure 1 |

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|----|---------------------------------------------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9 |
| 2 | | | | |
| 3 | | | | |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 9 |
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| 7 | Methods: Assignment of interventions (for controlled trials) | | | |
| 8 | | | | |
| 9 | Allocation: | | | |
| 10 | | | | |
| 11 | Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 11 |
| 12 | | | | |
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| 16 | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 11 |
| 17 | | | | |
| 18 | | | | |
| 19 | | | | |
| 20 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 11 |
| 21 | | | | |
| 22 | | | | |
| 23 | | | | |
| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| 25 | | | | |
| 26 | | | | |
| 27 | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 12 |
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| 31 | Methods: Data collection, management, and analysis | | | |
| 32 | | | | |
| 33 | Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11 and 12 |
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| 39 | | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | n/a |
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| 1 | Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 12 |
| 2 | Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 12 and 13 |
| 3 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13 |
| 4 | | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised), and any statistical methods to handle missing data (eg, multiple imputation) | 13 |
| 5 | Methods: Monitoring | | | |
| 6 | Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and references to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 14 |
| 7 | | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| 8 | Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 14 |
| 9 | Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
| 10 | Ethics and dissemination | | | |
| 11 | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 13 |
| 12 | Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 13 |

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| | | | | |
|----|-------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| 1 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32) | 10 |
| 2 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| 3 | | | | |
| 4 | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 12 |
| 5 | | | | |
| 6 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 1 |
| 7 | | | | |
| 8 | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 12 |
| 9 | | | | |
| 10 | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| 11 | | | | |
| 12 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 14 |
| 13 | | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| 14 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level datasets, and statistical code | n/a |
| 15 | | | | |
| 16 | Appendices | | | |
| 17 | | | | |
| 18 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorized surrogates | Figure 2 |
| 19 | | | | |
| 20 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |
| 21 | | | | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

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Different potencies of topical corticosteroids for a better treatment strategy in children with atopic dermatitis (the Rotterdam Eczema study): protocol for an observational cohort study with an embedded randomized open-label controlled trial

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| Keywords: | PRIMARY CARE, PAEDIATRICS, atopic dermatitis, randomized open-label controlled trial |

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2 **Different potencies of topical corticosteroids for a better treatment strategy in**
3 **children with atopic dermatitis (the Rotterdam Eczema study): protocol for an**
4 **observational cohort study with an embedded randomized open-label controlled**
5 **trial**

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15
16 *Authors' contributions*

17 G. Elshout, A.M. Bohnen and P.J.E. Bindels conceived the idea and secured funding.
18 Ethics applications were made by K.F. van Halewijn in collaboration with G. Elshout,
19 A.M. Bohnen and P.J.E. Bindels. S.G.M.A. Pasmans and P.J. van den Berg provided
20 intellectual input concerning study design and statistical analysis. All authors were
21 involved in drafting or critically revising this work, and in final approval of the version to
22 be published.

23
24 *Funding statement*

25 This research received no specific grant from any funding agency in the public,
26 commercial or not-for-profit sectors'.

27
28 *Competing interests*

29 There are no competing interests for any authors.

31 *Trial registration*

32 This trial was prospectively registered at the Netherlands National Trial Register (NTR:
33 6679).

34

35

36 **Abstract**

37 **Introduction**

38 Topical corticosteroids (TCS) of different potencies are the main treatment to control
39 atopic dermatitis (AD). The Dutch guideline on AD for general practitioners (GPs)
40 recommends a stepwise approach in which treatment steps are tailored to the severity
41 of the disease, starting with the lowest possible potency of TCS. However, it remains
42 unclear whether the recommended stepwise approach is most efficient. This
43 randomized open-label controlled trial aims to determine whether a potent TCS is more
44 effective than a low-potency TCS in the initial treatment of children with a moderate
45 flare-up of AD in primary care. In the observational cohort, the overall aim is to
46 determine the frequency, burden and determinants of flare-ups of AD during follow-up.

47

48 **Methods and Analysis**

49 The study is an observational cohort study with an embedded pragmatic randomized
50 controlled, open-label trial. Eligible are patients diagnosed with AD (aged 12 weeks to
51 18 years) who visited the GP for AD, or received repeated prescriptions for AD in the
52 previous 12 months; follow-up of the cohort is 1 year. Children are enrolled in the trial if
53 they have a flare-up of AD during follow-up in the cohort. Eligible children are
54 randomized to the intervention group (with a potent TCS once daily) or to the GP
55 guideline group (with a low potency TCS once daily). Primary outcome is the difference
56 in average subjective disease severity over 24 weeks follow-up in the trial, measured
57 with the Patient Oriented Eczema Measure (POEM). As secondary outcome, the
58 Eczema Area and Severity Index (EASI) is measured.

59

60 **Ethics and Dissemination**

61 This study tests the hypothesis that immediate treatment with a potent TCS during a

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3 62 flare-up of AD leads to faster and more efficacious results as compared to starting with
4 63 a TCS with low potency with less overall use of TCS. The study protocol is approved by
5 64 the Medical Ethics Committee (MEC) of the Erasmus Medical Center Rotterdam, the
6 65 Netherlands (MEC-2017-328). The results of the study will be published in international
7 66 peer-reviewed journals and presented at national and international conferences.
8
9 67
10
11
12 68 **Trial registration**
13 69 This trial was prospectively registered at the Netherlands National Trial Register (NTR)
14 70 under number 6679.
15
16
17
18
19 72 **Keywords**
20
21 73 Primary care, paediatrics, atopic dermatitis, cohort, randomized open-label controlled
22
23 74 trial
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25
26
27 76 **Strengths and limitations of this study**
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29
30 77 • This is the first study to investigate the effectiveness of initial treatment with TCS
31 78 class I vs class III for long-term control of atopic dermatitis in children in primary
32
33 79 care.
34
35
36 80 • Pragmatic treatment strategy in real-life clinical practice.
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38 81 • Study is performed in general practice, where most children with eczema are
39 82 treated.
40
41 83 • Cohort study on determinants of flare-up and disease burden of atopic dermatitis
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43 84 in children.
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45 85 • This randomized open-label trial may be prone to observation bias.
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1 2 3 86 **Introduction** 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

Atopic dermatitis (AD), or eczema, is a chronic, highly pruritic inflammatory skin disease and one of the most common skin disorders in children. (1) Eczema is in the top 10 of the most prevalent disorders in general practice in children aged up to 18 years.(2) The prevalence of AD has increased over the past 30 years.(3) It is estimated that 10-20% of children and 1-3% of adults in developed countries are affected by the disorder.(4) In the Netherlands, cumulative incidence of AD at age 18 years is at least 24%. (5) AD often starts in early infancy; about 45% of all cases begin within the first 6 months of life, 60% during the first year, and 85% before 5 years of age.(6) AD is associated with (later) occurrence of asthma and allergic rhinitis.(5)

The disorder results in significant morbidity and adversely affects quality of life. Factors that contribute to a poor quality of life are fatigue, itch, activity restriction, depression, and sleep deprivation.(7) Approximately 47-60% of children with AD experience sleep disturbance, (8) and children with AD and their parents can lose about 1-2 h of sleep/night.(9) Therefore, AD affects social functioning and psychological wellbeing, and has an even greater impact than diabetes on families of young patients. (9, 10) This includes direct and indirect financial costs, time spent on treatment, sleep deprivation (1-2 h/night) and physician visits.

Since there is no definitive cure for eczema, suppressive treatment aims to control the disease. The majority of patients in general practice control their symptoms by application of emollients accompanied by symptomatic anti-inflammatory therapy consisting of topical corticosteroids (TCS). (11) The Dutch guideline on AD for general practitioners (GPs) advocates a stepwise approach in which treatment steps are tailored to the severity of the disease, as determined using the Three Item Severity (TIS) score. (12) The choice of potency of corticosteroids is determined by estimating the required effect. When AD is mild to moderate, a mild (class I) to moderate potent (class II) TCS is preferred, while potent (class III) TCS is used only when AD is severe. When treatment is insufficient, a higher class can be used. Due to safety concerns, the Dutch

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3 117 GP guideline recommends to use the lowest potency possible that will still be effective
4 to treat the eczema. Potential local side-effects of CS are telangiectasia, atrophy,
5 hypopigmentation, and striae. However, the review of Siegfried et al. showed no
6 evidence of atrophy and supported the long-term safety of low and moderate TCS. (13)
7 121 Potential systemic effects of TCS may include suppression of the hypothalamic-
8 pituitary-adrenal (HPA) axis, and osteoporosis, glaucoma, cataract, and growth
9 reduction. Nevertheless, osteoporosis and growth reduction are not reported in studies
10 with long-term follow-up. (13-15).
11
12 125 The existing trials on the efficacy of TCS in children are often outdated and of inferior
13 quality with only a short follow-up. (16-18) However, they indicate that more potent TCS
14 may result in faster and better disease control in AD; nevertheless, it is not clear which
15 initial treatment strategy (i.e. mild or potent CS) is the best. (12, 19) During a flare-up,
16 treatment with a potent TCS might lead to faster and better results as compared to
17 starting with a mild TCS, with eventually less overall use of TCS. Besides improvements
18 in disease control and patients' satisfaction, this may also lead to fewer medical
19 consultations and prescriptions, and may therefore be more cost effective. The present
20 study focuses on these gaps and hopes to make an important contribution to knowledge
21 regarding the use of TCS in children with AD treated in general practice.
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36 135
37 136 **Objectives**
38 To determine whether initial treatment with a potent TCS is more effective than a mild
39 TCS in the treatment of children with a moderate flare-up of AD in primary care in the
40 short (i.e. 1 week and 4 weeks of follow-up) and long-term (i.e. 6 months follow-up)
41 control of the disease.
42
43 In the observational cohort, the aim is to determine the frequency and determinants of
44 flare-ups of AD. Furthermore, we will explore the burden of AD by measuring severity,
45 medication use, healthcare use and quality of life (QoL) during 1-year follow-up.
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53 145 **Study design**
54 146 The Rotterdam Eczema study is an observational cohort study with an embedded
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3 147 pragmatic randomized open-label superiority trial with two groups and a patient-reported
4 primary outcome of long-term control. See flowchart in figure 1.
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6 149
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8 150 **Methods; participants, interventions and outcomes**
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10 151 *Healthcare system*
11
12 152 The GP plays a key role in the Dutch healthcare system and (almost) everybody is
13 registered with a GP practice. Diagnosis and treatment of eczema, also in children, are
14 part of general practice. In case of diagnostic or treatment problems in children with
15 eczema, referral to secondary care is available; however, referral to a dermatologist is
16 not possible without the consent of a GP.
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18 156
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22 158 *Study setting*
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24 159 Children will be recruited from general practices located in the western part of the
25 Netherlands. The GPs will perform a search in their information system to identify
26 potentially eligible children.
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30 162
31 163 *Eligibility criteria*
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33 164 To be eligible to participate in the cohort study, a child must meet all of the following
34 criteria: aged between 12 weeks and 18 years, diagnosis of eczema (ICPC code S87
35 and S88 or prescription of topical treatment for eczema) plus confirmation of the
36 diagnosis by the GP, a consultation or repeated prescription in the previous 12 months,
37 and informed consent. Exclusion criteria for the cohort study are: as determined by the
38 own GP. The own GP will check the list of selected children, the own GP is aware of
39 potential problems limiting participation in a trial like family problems eg circumstances
40 such as ongoing problems due to divorcing parents, relevant psychosocial problems, a
41 seriously ill family member or if the child has serious comorbidities (eg intellectual
42 disability)..Furthermore, exclusion criteria are: currently under treatment with a
43 dermatologist, contra-indications for the study medication, language barrier, or no
44 access to internet (necessary to fill in weekly online questionnaire).
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46 175
47
48 176 The inclusion criteria for the trial part of the study are: participation in the cohort, flare-
49 up (i.e. need to intensify topical treatment) from the child's and/or parents' point of view,
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59 January 16th, 2019, version 2
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3 178 a Three Item Severity (TIS) score from ≥ 3 to < 6 . Exclusion criteria for the trial part are:
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5 179 use of TCS in the 2 weeks before inclusion in the trial, AD on eyelid(s), $> 50\%$ of body
6
7 180 affected by AD, other skin disorders hampering proper assessment of eczema,
8
9 181 pregnancy and or breastfeeding, or untreated skin infections (bacterial, viral, fungal or
10
182 parasitic).

11 183

12 184 *Interventions*

13 185 Eligible children will participate in the trial part if they have a flare-up of AD. They will be
14 186 randomized to either the **intervention group** or to the GP guideline group (**control**
15
187 **group**). Those allocated to the intervention group will receive a potent TCS class III
16
188 once daily to start with at each flare-up during the follow-up period of the trial. If children
17
189 are aged > 2 years, they will follow a predefined weaning-off scheme (i.e. reduction of
18
190 frequency) when their symptoms have improved. If children are aged < 2 years, they will
19
191 be reassessed by the GP after 1-2 weeks. When AD is improved but still needs
20
192 treatment, children will be treated according to the Dutch GP guideline (i.e. switch to a
21
193 less potent TCS).

22 194 Children in the control group will receive care as stated in the Dutch GP guideline for all
23 195 flare-ups during the trial period. First, they will start with a mild TCS class I once daily.
24 196 When not improved within 1-2 weeks, a mild potent TCS class II once daily will be
25
197 prescribed. When class II does not improve symptoms within 1-2 weeks, a potent TCS
26
198 class III will be prescribed once daily. When symptoms do improve, children will follow a
27
199 predefined weaning-off scheme. (12)

28 200 In the present study, hydrocortisone acetate cream 1%, and triamcinolone acetonide
29 201 cream 0.1% will be used as class I and class II TCS, respectively, since this is a
30
202 recommended preparation in the national guideline.(12) For class III TCS, fluticasone
31
203 propionate cream 0.05% will be used; this cream was chosen since it has a relatively
32
204 short half-time as compared to the class III TCS recommended by the national guideline
33
205 (i.e. betamethasone).(12) and is expected to limit potential side-effects. Children will
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206 receive the prescription from their own GP and will obtain the prescribed medication
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207 from the child's own pharmacy.

36 208 Besides the use of corticosteroids, all children (control and intervention group) will

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3 209 always be advised to use indifferent therapy with a standard emollient (i.e.
4 210 'cetomacrogol'). The advice is to use the emollients daily.
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8 211 *Patient and Public Involvement*
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10 212 The recommendations in the Dutch guideline are based on scientific research. It appears,
11 however, that research to support recommendations is sometimes lacking or inadequate. The
12 Dutch guideline states as a knowledge gap ('lacunebak') that it is not clear which treatment
13 strategy, mild or potent CS, is best when treating a flare-up of AD. (12) This stated knowledge
14 gap resulted in the research question of our study.
15
16 217 The outcome measures are based on the recommendations stated by the HOME-initiative.
17
18 218 During the development of the core outcome set and its measurement tools by this initiative,
19 patients have been intensively involved.
20
21 220 The burden of the intervention is similar to the control group, both groups will use cream.
22
23 221 Therefore, the burden of the intervention was not specifically discussed with patients.
24
25 222 Study participants will be informed about the results by a simplified summary send by email
26
27 223 Figure 1. Flow chart of the study.
28
29

30 224 **Outcomes**

31 225 **Primary outcome measure**

32 226 The primary outcome will be change in disease severity over 24-weeks follow-up in the
33 trial, as measured by the average score of the Patient-Oriented Eczema Measure
34 (POEM). POEM is a patient-reported outcome based on symptoms over the previous
35 week, which can be self-completed by the child's parent or the child. POEM is a
36 validated questionnaire and has been recommended by the Harmonizing Outcome for
37 Eczema (HOME) initiative as the preferred instrument to capture patient-reported
38 symptoms in eczema trials.(20) The POEM score is collected weekly in the trial part
39 over 24 weeks and, to measure long-term control, the difference between the two
40 treatment groups in the average POEM scores will be measured over these 24 weeks.
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236 **Secondary outcome measures**

237 The Eczema Area and Severity Index (EASI) will be used as objective measurement of
238 the AD. The EASI has been identified by the HOME initiative as the core outcome

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3 239 measurement instrument to evaluate clinical signs of AD in all future trials investigating
4 interventions for AD. (21) The EASI is scored by a physician and rates both the intensity
5 and extent of AD signs. The EASI will be used as secondary outcome in both the trial
6 and the cohort study. The EASI score is collected at baseline, and at weeks 1, 4 and 24
7 of the trial, and at baseline, and at weeks 26 and 52 in the cohort study. See table 1 for
8 an overview of observations made during the study.
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10 244
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14 245 Other secondary outcomes in the trial part include: i) changes in disease severity after 1
15 week and 4 weeks using POEM, ii) QoL using the Infants' Dermatitis Quality of Life
16 Index (IDQOL) or Children's Dermatology Life Quality Index (CDLQI) (depending on
17 age), iii) medication compliance (determined as a POEM >8 and use of TCS during that
18 week), iv) local side-effects (painful application, telangiectasia, atrophy,
19 hypopigmentation, and striae), v) time to recovery (i.e. time till start weaning-off
20 treatment), vi) frequency of flare-ups, vii) medication use (subjective and objective), viii)
21 patient global assessment and investigator global assessment (both on a 6-point scale;
22 clear, almost clear, mild, moderate, severe, very severe), ix) itch intensity score (the
23 numeric rating scale-11 is ranging from 0, no itch to 10, worst itch imaginable), and x)
24 healthcare use (i.e. telephone contact with GP, consultation at the general practice, or
25 referral to secondary care).
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3 268 Table 1. Schedule of observations made during the study
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| Outcomes collected | Cohort | | | Weekly for 52 weeks | Trial | | | Weekly for 24 weeks |
|-------------------------------------------------|----------|---------|---------|---------------------|----------|--------|---------|---------------------|
| | Baseline | Week 26 | Week 52 | | Baseline | Week 1 | Week 24 | |
| Proxy-reported/patient reported outcomes | | | | | | | | |
| Eczema severity over past week (POEM) | V | | | V | V | | | V |
| Eczema-related quality of life (IDQOL/CDLQI) | V | V | V | V | V | V | V | V |
| Flare-up | | | | V | | | | V |
| Amount of days emollients used in past week | | | | V | | | | V |
| Amount of days TCS used in past week | | | | V | | | | V |
| Use of medication other than TCS in past week | | | | V | | | | V |
| Adverse effects from treatment in past week | | | | V | | | | V |
| Doctor's visits in past week | | | | V | | | | V |
| Objective reported outcomes | | | | | | | | |
| Three Item Severity score | | | | | V | | | |
| Eczema area and severity (EASI) | V | V | V | | V | V | V | V |
| Weigth | | | | | V | V | V | V |
| Length | | | | | V | V | V | V |
| Head circumference | | | | | V | V | V | V |
| Weigh medication | | | | | V | | | |

269
270 POEM= Patient-Oriented Eczema Measure, EASI= Eczema Area and Severity Index, IDQOL= Infants' Dermatitis Quality
271 of Life Index , CDLQI= Children's Dermatology Life Quality Index ,TCS= Topical corticosteroid, PG= Patient global
272 assessment, IGA= Investigator global assessment

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3 273 **Sample size**

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5 274 In this study, we based our sample size calculation on the minimal clinically important
6 difference (MCID) of the POEM in young children with eczema as determined by Gaunt
7 at al.(24) The MCID is the smallest change in an outcome measure that represents a
8 clinically relevant outcome. A treatment effect of 3.0 POEM points was considered
9 clinically relevant. We used a mean of 128.8 (SD of 5.9) as presented in trials with a
10 similar population (i.e. primary care patients) on baseline POEM characteristics. (24)
11
12 280 Taking these numbers into account, with a power of 80% and $\alpha=0.05$ (2-sided) we need
13 61 children per trial group. Assuming a dropout rate of 15% during the study, 72
14 children per treatment arm are required.
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283
284 **Recruitment**

285 Based on Dutch GP data and an expected patient participation of 50%, per participating
286 GP we expect to include 7 children per year for the cohort, and 4 in the trial (based on
287 flare-ups). (2) Therefore, we expect to need about 36 participating GPs. First, we will
288 collaborate with our academic network named PRIMEUR. The academic PRIMEUR
289 network includes 13 centers with about 97 participating GPs and about 160,000
290 patients. If the inclusion is behind expectations, more GPs will be invited to participate in
291 the study. Furthermore, if inclusion still remains behind expectations using the search
292 protocol (e.g. consultation, or repeated prescription in the previous 12 months) we will
293 expand the search period from 12 to 24 months.

294 Children will be recruited from general practices. When a GP decides to participate, the
295 GP will perform a search in their information system to identify all possible eligible
296 children. Invitation letters to participate (in the name of the GP) will be sent to the
297 parent/carer of the children.

298 Children are asked to respond using a response card or response e-mail, irrespective of
299 whether or not they are willing to participate. These responses are sent to the
300 coordinating researcher of the department of General Practice, Erasmus Medical Center
301 Rotterdam.

302 After receiving a positive response from the child, the research assistant will have

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3 303 telephone contact with the child (this can be with the parents if the child is aged ≤ 12
4 years, or the children themselves). During this telephone contact, additional information
5 on the study and study procedures will be explained. Based on the telephone contact, if
6 the child is eligible and is still interested in participating, the patient information letter
7 (PIF) will be sent by mail. Afterwards, if the child is willing to participate, the informed
8 consent will be signed by the parents (if the child is aged ≤ 16) or the child (when aged
9 ≥12 years) and sent to the department of General Practice.
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15 310 After receiving the signed PIF, the research assistant will contact the general practice of
16 the child to inform them about the child's participation. The GP practice will contact the
17 parents of the child to arrange a consultation. During this first consult with the physician
18 assistant, the baseline EASI will be obtained.
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25 314
26 **Assignment of interventions**
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28 315 When the AD flares up, the child (or the child's parents) has to make an appointment by
29 the GP. The definition of a flare-up is the need to intensify topical treatment from the
30 patient's and/or parents' point of view
31

32 316 If the child has a flare-up of AD and is eligible for inclusion in the trial, the child will be
33 randomly allocated to one of the two groups by the physician assistant of their own GP,
34 using the data management system (Research manager). The randomization list will be
35 computer-generated and unknown to the investigators.
36
37

38 317 Children will be stratified by TIS score (i.e. TIS score 3, 4 and 5) to ensure equal
39 distribution of the severity of AD between the intervention and control group. Random
40 permuted blocks of two will be generated. The GP will prescribe the medication of
41 randomization.
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44 327
45 **Data collection and methods**
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47 328 Data collection of the patient-reported outcomes and the objective reported outcomes
48 will be carried out using online case report forms. Children (or the child's parents) will
49 receive a reminder by email if questionnaires are not filled in after a standardized
50 interval of three days. If questionnaires are not filled in at key time points, participants
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3 333 will receive a telephone reminder. Children will receive a small gift after completing the
4 cohort or trial follow-up. The weekly questionnaires include a question on who
5 completed the questionnaire, the child, the parent or together. We can therefore take
6 into account by whom the questionnaire has been completed in our analysis. If patients
7 are 16 years or older, they will complete the questionnaires themselves. Children under
8 16 are free in their choice to complete the questionnaire themselves or together with /
9 by a parent. The physician assistants will received additional training in the
10 pathophysiology and treatment of AD and in scoring the EASI.
11
12 341
13
14 342 **Data management**
15 Data will be handled confidentially and anonymously. A child's identification code is
16 used to link the data to the child; a unique code is randomly generated for each
17 individual. The principal investigator safeguards the key to the code.
18 The software program Research Manager will be used for the online questionnaires and
19 the childrens' personal data, respectively.
20
21 348
22
23
24 349 **Statistical methods**
25 All analyses of the primary study parameters will be performed according to the
26 intention-to-treat principle (ITT), i.e. irrespective of compliance. Those who perform the
27 analyses will be kept blind regarding which group has received what kind of treatment.
28
29 350 Secondary, a per-protocol analysis, excluding children in whom major violations of the
30 protocol have occurred, will also be performed. Major protocol violations are: withdrawal
31 from study or loss to follow-up, and medication compliance <75%.
32
33 351 In case major events occur during the study period that necessitate withdrawal from
34 study, or loss-to-follow-up/dropout for other reasons, weekly diary card data will be
35 evaluated up to the week of such dropout. However, children are requested to agree
36 with further follow-up according to the study protocol (e.g. weekly questionnaires).
37
38 352 Medication compliance <75%, (also called non-compliance) is determined as a POEM
39 >8 and no use of TCS during that week; the compliance is determined per week.
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3 362 For the primary outcome, statistical comparison between the treatment groups will be
4 363 done using analysis of covariance (ANCOVA) including the covariates: baseline
5 364 symptom score, age, and gender. Treatment effects will be tested two-sided with a
6 365 significance level of 5%.
7
8 366 For the main study parameter, it is essential that the weekly diaries are filled in
9 367 adequately. However, in case of missing data, these will be imputed using multiple
10 368 imputation; this is considered the most appropriate way of dealing with missing data.
11 369 (25) Missing values of the POEM will be imputed 10 times using the multivariate
12 370 imputation by chained equations (MICE) logarithm (R-Project). The imputation model
13 371 included sex, age, type of medication used and frequency of application, and the
14 372 outcome measure POEM.
15
16 373 Secondary outcomes of the trial, statistical comparison between the treatment groups
17 374 for changes in disease severity, and QoL after 1 week and 4 weeks, will be performed
18 375 using ANCOVA, including the covariates baseline symptom score, age and gender. The
19 376 other secondary outcomes (i.e. local side-effects, systemic side-effects, compliance,
20 377 frequency of flare-ups, medication use and healthcare use) will be analyzed with linear
21 378 or logistic regression when appropriate. For the time to recovery, Cox regression
22 379 analyses will be performed.
23
24 380 To explore differences in patient and disease characteristics in the two treatment arms,
25 381 and to determine which factors are related to compliance to the two treatment
26 382 strategies, backward logistic regression will be used.
27
28 383 Patient characteristics to be examined are: age, sex, age at presentation of AD, history
29 384 of atopy (i.e. asthma, allergic rhinitis, food allergy and anaphylaxis), use of other CS (i.e.
30 385 nasal, inhaled, oral), and QoL (IDQoL, CDLQI). Disease characteristics are disease
31 386 severity (POEM and EASI), duration of AD, location of AD (i.e. head and neck, upper
32 387 limbs, lower limbs and trunk, all extracted from EASI) and previous medical care (i.e. no
33 388 previous treatment, GP only, GP and secondary care).
34
35 389 To explore which factors are related to compliance to the two treatment strategies,
36 390 backward logistic regression will be used. The factors to be explored are treatment arm,
37 391 age, sex, age at presentation of AD, disease severity (POEM and EASI), duration of
38 392 AD, use of other CS (i.e. nasal, inhaled, oral), and QoL (IDQoL, CDLQI).

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3 393 The secondary outcomes for the cohort will be analyzed with descriptive statistics (i.e.
4 disease severity, frequency of flare-ups, medication use, healthcare use, QoL).
5 394 Analyses to determine what the determinants of flare-ups of AD are after 1-year follow-
6 up will be performed with logistic regression analyses.
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11 398 **Ethics and dissemination**
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13 399 The study protocol is approved by the Medical Ethics Committee (MEC) of the Erasmus
14 400 Medical Center Rotterdam, the Netherlands (MEC-2017-328).
15 401 Amendments are changes made to the research protocol after a favorable opinion from
16 the accredited MEC. All substantial amendments will be notified to the MEC and to the
17 competent authority.
18 402
19 403
20 404 The results of the study will be published in international peer-reviewed journals and
21 presented at (inter)national conferences. We aim to publish several peer-reviewed
22 publications on the best treatment strategy in children with AD related to patient-
23 oriented outcomes, healthcare consumption, and side-effects. The results of this study
24 may be implemented into clinical practice and/or can be used for the next update of the
25 Dutch guideline on AD for GPs.
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33 412 **Safety reporting**
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35 413 In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the
36 414 study if there is sufficient ground that continuation of the study will jeopardise subject
37 415 health or safety. The sponsor will notify the accredited METC without undue delay of a
38 416 temporary halt including the reason for such an action. The study will be suspended
39 417 pending a further positive decision by the accredited METC. The investigator will take
40 418 care that all subjects are kept informed.
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43 421 **Monitoring**
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45 422 Due to the characteristics of this study it is not necessary to install a Data Safety
46 423 Monitoring Board. Nevertheless, the study will be monitored as described in the ICH-
47 424 GCP Guidelines (chapter 5.18). The department of General Practice has developed a
48 425 monitoring plan and monitoring checklist (based on the ICH-GCP Guidelines) which will
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3 424 be used in this study. A senior researcher (project leader) will be designated as monitor.
4 425 This senior researcher is not related to the current project and is part of another
5 research discipline within the department. At various moments in the study (not known
6 to the researcher in front) an appointment will be made with the researcher and
7 projectleader of the current project to monitor the study by making use of the checklist
8 of the department of general practice.
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17 431 **Adverse events**
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19 432 All (serious) adverse events and suspected unexpected serious adverse reactions
20 reported spontaneously by the subject or observed by the investigator or the staff will be
21 recorded.
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26 436 **Discussion**
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28 437 This will be the first study to investigate the effectiveness of treatment with TCS class I
29 vs class III on long-term control over 6-months follow-up of children in primary care with
30 AD.
31
32 440 We chose an observational cohort design with an embedded pragmatic randomized
33 open-label trial, as it might be difficult to randomize children in primary care at the
34 moment they present with a flare-up. The observational cohort gives the opportunity to
35 follow the course of AD in children in primary care with regard to the frequency and
36 determinants of flare-ups, and the burden of disease. As primary outcome, we chose a
37 clinical outcome relevant to patients. In AD, the appearance of the skin does not always
38 closely reflect the subjective symptoms, i.e. when the latter causes a major impact on
39 the child and family. (9, 10) Therefore, it was particularly important to design a trial with
40 a validated participant-reported primary outcome.
41
42 449 The structure of regular home visits will probably artificially improve treatment
43 adherence. It is generally known that treatment adherence is highest immediately after
44 seeing a doctor. (26) Both treatment arms will receive home visits, so this effect will be
45 equally spread. The home visits will influence the generalizability of the results.
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47 453 However, it is crucial for several outcome measures to visit the patients. We kept the
48 frequency of home visits to a minimum, balancing the unwanted effect of better
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3 455 treatment adherence and gathering important information on study outcomes.
4 456 A limitation of the study is the open-label design. Since participants know which
5 457 treatment arm they will be assigned to, they cannot be blinded to the intervention. Also,
6 458 because the GP must be able to adjust the treatment strategy or refer the child if
7 459 required, the GP cannot be blinded. The research assistants will also be aware of the
8 460 medication use of the child, as they have to register and weigh the medication.
9 461 Given that our primary outcome is patient-reported, the additional costs for blinding
10 462 researchers to collect the objective data (i.e. EASI) did not seem justifiable.
11 463 Concerns have been reported about the safety of TCS application in children with
12 464 regard to incorrect application. (27) Potential local side-effects of TCS are painful
13 465 application, telangiectasia, atrophy, hypopigmentation, and striae. However, there is a
14 466 lack of evidence from good quality research concerning these local side-effects of TCS.
15 467 (28) Nevertheless, in a study on children with AD with a follow-up of 18 weeks, no
16 468 difference was found in skin atrophy in children using class-III TCS for 3 days per week
17 469 vs children using class I TCS. (16) Potential systemic effects of TCS may include
18 470 suppression of the HPA axis, and osteoporosis, glaucoma, cataract, and growth
19 471 reduction. Although there is lack of evidence about these potential systemic side-
20 472 effects, it is reported that topical TCS has little to no effect on the HPA axis,
21 473 osteoporosis and growth reduction. (12, 14, 15, 29) In addition, the treatment scheme
22 474 for the class III TCS is within the recommended dosage of the Dutch guideline on AD.
23 475 (12) Additionally, we want to include children of all ages with atopic dermatitis on most
24 476 widespread areas. Therefore, we chose a strong topical corticosteroid with the most favorable
25 477 profile, this is found in fluticasone propionate 0.05% or 0.005% since it has a relatively
26 478 short half-life as compared to the class III TCS that is recommended by the Dutch
27 479 guideline (i.e. betamethasone). (12)
28 480 In this way, we aim to further reduce the already low risk of potential (systemic) side-
29 481 effects; therefore, we believe that it is safe to use a class III TCS according to the
30 482 previously described treatment scheme.
31 483 Experience from dermatologists indicate that starting with a high-dose TCS leads to a
32 484 faster and better result as compared to starting with a low-dose TCS. However, most
33 485 children with AD are treated by a GP (only about 1% is referred to secondary care) and

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2
3 486 have a milder form of AD as compared to patients treated by a dermatologist. (2)
4 487 Whether the effects of initial treatment with a potent TCS as experienced in a specialist
5 488 setting can be transferred to treatment in primary care is unknown. Since the present
6 489 study will focus on these gaps, it will hopefully make an important contribution to
7 490 knowledge with respect to the use of local corticosteroids in children with AD treated in
8 491 general practice.
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17 493 **Figure legend**
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19 494 Figure 1: GP= General practitioner, EASI= Eczema Area and Severity Index, POEM=
20 495 Patient-Oriented Eczema Measure, AD= atopic dermatitis, TCS= Topical corticosteroid,
21 496 PGA= Patient global assessment
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497 REFERENCES

- 500 1. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric
501 population. *Pediatrics* 2008;122(4):812-824.
- 502 2. JCC Braspenning FS, RPTM Grol (redactie). Tweede Nationale Studie naar ziekten en
503 verrichtingen in de huisartspraktijk. Kwaliteit huisartsenzorg belicht. Utrecht/Nijmegen: NIVEL/WOK;
504 2004.
- 505 3. Watson W, Kapur S. Atopic dermatitis. *Allergy Asthma Clin Immunol* 2011;7 Suppl 1:S4.
- 506 4. Larsen FS, Hanifin JM. Epidemiology of atopic dermatitis. *Immunology and Allergy Clinics of
507 North America* 2002;22(1):1-24.
- 508 5. Pols DHJ, Nielen MMJ, Korevaar JC, Bindels PJE, Bohnen AM. Reliably estimating prevalences of
509 atopic children: an epidemiological study in an extensive and representative primary care database. *NPJ
510 Prim Care Respir Med* 2017;27(1):23.
- 511 6. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358(14):1483-1494.
- 512 7. Tollefson MM, Bruckner AL, Section On D. Atopic dermatitis: skin-directed management.
513 *Pediatrics* 2014;134(6):e1735-1744.
- 514 8. Chang YS, Chou YT, Lee JH, Lee PL, Dai YS, Sun C, et al. Atopic dermatitis, melatonin, and sleep
515 disturbance. *Pediatrics* 2014;134(2):e397-405.
- 516 9. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial
517 cost. *Arch Dis Child* 1997;76(2):159-162.
- 518 10. Barbeau M, Bpharm HL. Burden of Atopic dermatitis in Canada. *Int J Dermatol* 2006;45(1):31-36.
- 519 11. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health
520 Technol Assess* 2000;4(37):1-191.
- 521 12. Dirven-Meijer PC DKC, Nonneman MGM, Van Sleeuwen D, De Witt-de Jong AWF, Burgers JS,
522 Opstelten W, De Vries CJH. NHG-Standaard Eczeem. *Huisarts wet* 2014;57(5):240-252.
- 523 13. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term
524 safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic
525 dermatitis. *BMC Pediatr* 2016;16:75.
- 526 14. van Velsen SG, Knol MJ, van Eijk RL, de Vroede MA, de Wit TC, Lam MG, et al. Bone mineral
527 density in children with moderate to severe atopic dermatitis. *J Am Acad Dermatol* 2010;63(5):824-831.
- 528 15. Thomas MW, Panter AT, Morrell DS. Corticosteroids' effect on the height of atopic dermatitis
529 patients: a controlled questionnaire study. *Pediatr Dermatol* 2009;26(5):524-528.
- 530 16. Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S, et al. Randomised controlled trial of
531 short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children
532 with mild or moderate atopic eczema. *Bmj* 2002;324(7340):768.
- 533 17. Kirkup ME, Birchall NM, Weinberg EG, Helm K, Kennedy CT. Acute and maintenance treatment
534 of atopic dermatitis in children - two comparative studies with fluticasone propionate (0.05%) cream. *J
535 Dermatolog Treat* 2003;14(3):141-148.
- 536 18. Vernon HJ, Lane AT, Weston W. Comparison of mometasone furoate 0.1% cream and
537 hydrocortisone 1.0% cream in the treatment of childhood atopic dermatitis. *J Am Acad Dermatol*
538 1991;24(4):603-607.
- 539 19. (SIGN) SIGN. Management of atopic eczema in primary care. Edinburgh: SIGN. SIGN publication
540 no. 125 March 2011(Available from URL: <http://www.sign.ac.uk>).
- 541 20. Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-
542 Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a
543 Harmonising Outcome Measures for Eczema (HOME) statement. *Br J Dermatol* 2017;176(4):979-984.

- 1
2
3 544 21. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome
4 Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin
5 Immunol* 2014;134(4):800-807.
6 547 22. Salek MS, Jung S, Brincat-Ruffini LA, MacFarlane L, Lewis-Jones MS, Basra MK, et al. Clinical
7 experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-
8 549 2012. *Br J Dermatol* 2013;169(4):734-759.
9 550 23. Basra MK, Gada V, Ungaro S, Finlay AY, Salek SM. Infants' Dermatitis Quality of Life Index: a
10 decade of experience of validation and clinical application. *Br J Dermatol* 2013;169(4):760-768.
11 552 24. Gaunt DM, Metcalfe C, Ridd M. The Patient-Oriented Eczema Measure in young children:
12 responsiveness and minimal clinically important difference. *Allergy* 2016;71(11):1620-1625.
13 554 25. Groenwold RH, Donders AR, Roes KC, Harrell FE, Jr., Moons KG. Dealing with missing outcome
14 data in randomized trials and observational studies. *Am J Epidemiol* 2012;175(3):210-217.
15 556 26. Feldman SR, Camacho FT, Krejci-Manwaring J, Carroll CL, Balkrishnan R. Adherence to topical
16 therapy increases around the time of office visits. *J Am Acad Dermatol* 2007;57(1):81-83.
17 558 27. Aubert-Wastiaux H, Moret L, Le Rhun A, Fontenoy AM, Nguyen JM, Leux C, et al. Topical
18 corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. *Br J Dermatol*
19 560 2011;165(4):808-814.
20 561 28. Callen J, Chamlin S, Eichenfield LF, Ellis C, Girardi M, Goldfarb M, et al. A systematic review of
21 the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007;156(2):203-221.
22 563 29. Friedlander SF, Hebert AA, Allen DB, Fluticasone Pediatrics Safety Study G. Safety of fluticasone
23 propionate cream 0.05% for the treatment of severe and extensive atopic dermatitis in children as
24 young as 3 months. *J Am Acad Dermatol* 2002;46(3):387-393.
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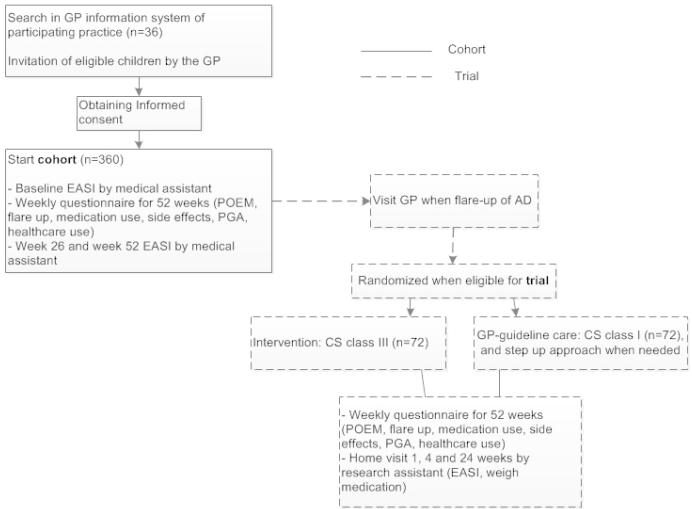


Figure 1. Flow chart of the study.

90x90mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|-----------------------------------|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | 3 | Date and version identifier | footer |
| Funding | 4 | Sources and types of financial, material, and other support | 1 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |

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bmjopen-2018-027392 on 19 June 2019. Downloaded from http://bmjopen.bmj.com/ on 10 June 2025. At Agency Enseignement Supérieur (ABES) AI training, and similar technologies. Bibliographie de I

1 Introduction

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|---|--------------------------|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 2 | Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4 and 5 |
| 3 | | 6b | Explanation for choice of comparators | 5 |
| 4 | Objectives | 7 | Specific objectives or hypotheses | 5 |
| 5 | Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, cluster, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 and 6 |

14 Methods: Participants, interventions, and outcomes

| | | | | |
|----|----------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| 16 | Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of study sites where data will be collected. Reference to where list of study sites can be obtained | 6 |
| 17 | | | | |
| 18 | Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6 |
| 19 | | | | |
| 20 | Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7 |
| 21 | | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | n/a |
| 22 | | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 9 |
| 23 | | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| 24 | | | | |
| 25 | Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variables (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8 and 9 |
| 26 | | | | |
| 27 | Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | figure 1 |
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| 1 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9 |
| 2 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 9 |

Methods: Assignment of interventions (for controlled trials)

Allocation:

| | | | | |
|----|----------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 10 | Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 11 |
| 11 | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 11 |
| 12 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 11 |
| 13 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| 14 | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 12 |

Methods: Data collection, management, and analysis

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|----|-------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 33 | Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11 and 12 |
| 34 | | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | n/a |

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|----|---------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1 | Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 12 |
| 2 | | | | |
| 3 | Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 12 and 13 |
| 4 | | | | |
| 5 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13 |
| 6 | | | | |
| 7 | | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised), and any statistical methods to handle missing data (eg, multiple imputation) | 13 |
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| 14 | Methods: Monitoring | | | |
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| 16 | Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and references to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 14 |
| 17 | | | | |
| 18 | | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| 19 | | | | |
| 20 | | | | |
| 21 | Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 14 |
| 22 | | | | |
| 23 | Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
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| 32 | Ethics and dissemination | | | |
| 33 | | | | |
| 34 | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 13 |
| 35 | | | | |
| 36 | | | | |
| 37 | Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 13 |
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| 1 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32) | 10 |
| 2 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| 3 | | | | |
| 4 | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 12 |
| 5 | | | | |
| 6 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 1 |
| 7 | | | | |
| 8 | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 12 |
| 9 | | | | |
| 10 | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| 11 | | | | |
| 12 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 14 |
| 13 | | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| 14 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level datasets, and statistical code | n/a |
| 15 | | | | |
| 16 | Appendices | | | |
| 17 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorized surrogates | Figure 2 |
| 18 | | | | |
| 19 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |
| 20 | | | | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

BMJ Open

Different potencies of topical corticosteroids for a better treatment strategy in children with atopic dermatitis (the Rotterdam Eczema study): protocol for an observational cohort study with an embedded randomized open-label controlled trial

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2 1 **Different potencies of topical corticosteroids for a better treatment strategy in**
3 2 **children with atopic dermatitis (the Rotterdam Eczema study): protocol for an**
4 3 **observational cohort study with an embedded randomized open-label controlled**
5 4 **trial**

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15
16 *Authors' contributions*

17 G. Elshout, A.M. Bohnen and P.J.E. Bindels conceived the idea and secured funding.
18 Ethics applications were made by K.F. van Halewijn in collaboration with G. Elshout,
19 A.M. Bohnen and P.J.E. Bindels. S.G.M.A. Pasmans and P.J. van den Berg provided
20 intellectual input concerning study design and statistical analysis. All authors were
21 involved in drafting or critically revising this work, and in final approval of the version to
22 be published.

23
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25 This research received no specific grant from any funding agency in the public,
26 commercial or not-for-profit sectors'.

27
28 *Competing interests*

29 There are no competing interests for any authors.

31 *Trial registration*

32 This trial was prospectively registered at the Netherlands National Trial Register (NTR:
33 6679).

34

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36 **Abstract**

37 **Introduction**

38 Topical corticosteroids (TCS) of different potencies are the main treatment to control
39 atopic dermatitis (AD). The Dutch guideline on AD for general practitioners (GPs)
40 recommends a stepwise approach in which treatment steps are tailored to the severity
41 of the disease, starting with the lowest possible potency of TCS. However, it remains
42 unclear whether the recommended stepwise approach is most efficient. This
43 randomized open-label controlled trial aims to determine whether a potent TCS is more
44 effective than a low-potency TCS in the initial treatment of children with a moderate
45 flare-up of AD in primary care. In the observational cohort, the overall aim is to
46 determine the frequency, burden and determinants of flare-ups of AD during follow-up.

47

48 **Methods and Analysis**

49 The study is an observational cohort study with an embedded pragmatic randomized
50 controlled, open-label trial. Eligible are patients diagnosed with AD (aged 12 weeks to
51 18 years) who visited the GP for AD, or received repeated prescriptions for AD in the
52 previous 12 months; follow-up of the cohort is 1 year. Children are enrolled in the trial if
53 they have a flare-up of AD during follow-up in the cohort. Eligible children are
54 randomized to the intervention group (with a potent TCS once daily) or to the GP
55 guideline group (with a low potency TCS once daily). Primary outcome is the difference
56 in average subjective disease severity over 24 weeks follow-up in the trial, measured
57 with the Patient Oriented Eczema Measure (POEM). As secondary outcome, the
58 Eczema Area and Severity Index (EASI) is measured.

59

60 **Ethics and Dissemination**

61 This study tests the hypothesis that immediate treatment with a potent TCS during a

1
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3 62 flare-up of AD leads to faster and more efficacious results as compared to starting with
4 63 a TCS with low potency with less overall use of TCS. The study protocol is approved by
5 64 the Medical Ethics Committee (MEC) of the Erasmus Medical Center Rotterdam, the
6 65 Netherlands (MEC-2017-328). The results of the study will be published in international
7 66 peer-reviewed journals and presented at national and international conferences.
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12 69 **Trial registration**
13 70 This trial was prospectively registered at the Netherlands National Trial Register (NTR)
14 71 under number 6679.
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21 73 **Keywords**
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23 74 Primary care, paediatrics, atopic dermatitis, cohort, randomized open-label controlled
24 75 trial
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29 77 **Strengths and limitations of this study**
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31
32 78 • This is the first study to investigate the effectiveness of initial treatment with TCS
33 79 class I vs class III for long-term control of atopic dermatitis in children in primary
34 80 care.
35
36
37 81 • Pragmatic treatment strategy in real-life clinical practice.
38
39 82 • Study is performed in general practice, where most children with eczema are
40 83 treated.
41
42 84 • Cohort study on determinants of flare-up and disease burden of atopic dermatitis
43 85 in children.
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45 86 • This randomized open-label trial may be prone to observation bias.
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1 2 3 87 **Introduction**

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7 Atopic dermatitis (AD), or eczema, is a chronic, highly pruritic inflammatory skin disease
8 and one of the most common skin disorders in children. (1) Eczema is in the top 10 of
9 the most prevalent disorders in general practice in children aged up to 18 years.(2) The
10 prevalence of AD has increased over the past 30 years.(3) It is estimated that 10-20%
11 of children and 1-3% of adults in developed countries are affected by the disorder.(4) In
12 the Netherlands, cumulative incidence of AD at age 18 years is at least 24%. (5) AD
13 often starts in early infancy; about 45% of all cases begin within the first 6 months of life,
14 60% during the first year, and 85% before 5 years of age.(6) AD is associated with
15 (later) occurrence of asthma and allergic rhinitis.(5)

16
17 98
18 99 The disorder results in significant morbidity and adversely affects quality of life. Factors
19 that contribute to a poor quality of life are fatigue, itch, activity restriction, depression,
20 and sleep deprivation.(7) Approximately 47-60% of children with AD experience sleep
21 disturbance, (8) and children with AD and their parents can lose about 1-2 h of
22 sleep/night.(9) Therefore, AD affects social functioning and psychological wellbeing, and
23 has an even greater impact than diabetes on families of young patients. (9, 10) This
24 includes direct and indirect financial costs, time spent on treatment, sleep deprivation
25 (1-2 h/night) and physician visits.
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28 107
29 108 Since there is no definitive cure for eczema, suppressive treatment aims to control the
30 disease. The majority of patients in general practice control their symptoms by
31 application of emollients accompanied by symptomatic anti-inflammatory therapy
32 consisting of topical corticosteroids (TCS). (11) The Dutch guideline on AD for general
33 practitioners (GPs) advocates a stepwise approach in which treatment steps are tailored
34 to the severity of the disease, as determined using the Three Item Severity (TIS) score.
35 (12) The choice of potency of corticosteroids is determined by estimating the required
36 effect. When AD is mild to moderate, a mild (class I) to moderate potent (class II) TCS
37 is preferred, while potent (class III) TCS is used only when AD is severe. When
38 treatment is insufficient, a higher class can be used. Due to safety concerns, the Dutch
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3 118 GP guideline recommends to use the lowest potency possible that will still be effective
4 to treat the eczema. Potential local side-effects of CS are telangiectasia, atrophy,
5 hypopigmentation, and striae. However, the review of Siegfried et al. showed no
6 evidence of atrophy and supported the long-term safety of low and moderate TCS. (13)
7 122 Potential systemic effects of TCS may include suppression of the hypothalamic-
8 pituitary-adrenal (HPA) axis, and osteoporosis, glaucoma, cataract, and growth
9 reduction. Nevertheless, osteoporosis and growth reduction are not reported in studies
10 with long-term follow-up. (13-15).
11
12 126 The existing trials on the efficacy of TCS in children are often outdated and of inferior
13 quality with only a short follow-up. (16-18) However, they indicate that more potent TCS
14 may result in faster and better disease control in AD; nevertheless, it is not clear which
15 initial treatment strategy (i.e. mild or potent CS) is the best. (12, 19) During a flare-up,
16 treatment with a potent TCS might lead to faster and better results as compared to
17 starting with a mild TCS, with eventually less overall use of TCS. Besides improvements
18 in disease control and patients' satisfaction, this may also lead to fewer medical
19 consultations and prescriptions, and may therefore be more cost effective. The present
20 study focuses on these gaps and hopes to make an important contribution to knowledge
21 regarding the use of TCS in children with AD treated in general practice.
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36 137 **Objectives**
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38 138 To determine whether initial treatment with a potent TCS is more effective than a mild
39 TCS in the treatment of children with a moderate flare-up of AD in primary care in the
40 short (i.e. 1 week and 4 weeks of follow-up) and long-term (i.e. 6 months follow-up)
41 control of the disease.
42
43
44 142 In the observational cohort, the aim is to determine the frequency and determinants of
45 flare-ups of AD. Furthermore, we will explore the burden of AD by measuring severity,
46 medication use, healthcare use and quality of life (QoL) during 1-year follow-up.
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52 146 **Study design**
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54 147 The Rotterdam Eczema study is an observational cohort study with an embedded
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3 148 pragmatic randomized open-label superiority trial with two groups and a patient-reported
4 primary outcome of long-term control. See flowchart in figure 1.
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8 151 **Methods; participants, interventions and outcomes**
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10 152 *Healthcare system*
11
12 153 The GP plays a key role in the Dutch healthcare system and (almost) everybody is
13 registered with a GP practice. Diagnosis and treatment of eczema, also in children, are
14 part of general practice. In case of diagnostic or treatment problems in children with
15 eczema, referral to secondary care is available; however, referral to a dermatologist is
16 not possible without the consent of a GP.
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22 159 *Study setting*
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24 160 Children will be recruited from general practices located in the western part of the
25 Netherlands. The GPs will perform a search in their information system to identify
26 potentially eligible children.
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31 164 *Eligibility criteria*
32
33 165 To be eligible to participate in the cohort study, a child must meet all of the following
34 criteria: aged between 12 weeks and 18 years, diagnosis of eczema (ICPC code S87
35 and S88 or prescription of topical treatment for eczema) plus confirmation of the
36 diagnosis by the GP, a consultation or repeated prescription in the previous 12 months,
37 and informed consent. This will be checked by the own GP and the researcher.
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41 170 Exclusion criteria for the cohort study are: as determined by the own GP. The own GP
42 will check the list of selected children, the own GP is aware of potential problems
43 limiting participation in a trial like family problems eg circumstances such as ongoing
44 problems due to divorcing parents, relevant psychosocial problems, a seriously ill family
45 member or if the child has serious comorbidities (eg intellectual disability). Furthermore,
46 exclusion criteria are: currently under treatment with a dermatologist, contra-indications
47 for the study medication, language barrier, or no access to internet (necessary to fill in
48 weekly online questionnaire).
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3 178 The inclusion criteria for the trial part of the study are: participation in the cohort, flare-
4 up (i.e. need to intensify topical treatment) from the child's and/or parents' point of view,
5 179 a Three Item Severity (TIS) score from ≥ 3 to < 6 . Exclusion criteria for the trial part are:
6 180 use of TCS in the 2 weeks before inclusion in the trial, AD on eyelid(s), $> 50\%$ of body
7 181 affected by AD, other skin disorders hampering proper assessment of eczema,
8 182 pregnancy and or breastfeeding, or untreated skin infections based on clinical signs and
9 183 symptoms (bacterial, viral, fungal or parasitic).
10 184
11 185
12 186 *Interventions*
13 187 Eligible children will participate in the trial part if they have a flare-up of AD. They will be
14 188 randomized to either the **intervention group** or to the GP guideline group (**control
15 group**). Those allocated to the intervention group will receive a potent TCS class III
16 once daily to start with at each flare-up during the follow-up period of the trial. If children
17 are aged > 2 years, they will follow a predefined weaning-off scheme (i.e. reduction of
18 frequency) when their symptoms have improved. If children are aged < 2 years, they will
19 be reassessed by the GP after 1-2 weeks. When AD is improved but still needs
20 treatment, children will be treated according to the Dutch GP guideline (i.e. switch to a
21 less potent TCS).
22
23 196 Children in the control group will receive care as stated in the Dutch GP guideline for all
24 flare-ups during the trial period. First, they will start with a mild TCS class I once daily.
25 197 When not improved within 1-2 weeks, a mild potent TCS class II once daily will be
26 prescribed. When class II does not improve symptoms within 1-2 weeks, a potent TCS
27 class III will be prescribed once daily. When symptoms do improve, children will follow a
28 predefined weaning-off scheme. (12)
29
30 202 In the present study, hydrocortisone acetate cream 1%, and triamcinolone acetonide
31 cream 0.1% will be used as class I and class II TCS, respectively, since this is a
32 recommended preparation in the national guideline.(12) For class III TCS, fluticasone
33 propionate cream 0.05% will be used; this cream was chosen since it has a relatively
34 short half-time as compared to the class III TCS recommended by the national guideline
35 (i.e. betamethasone).(12) and is expected to limit potential side-effects. Children will
36 receive the prescription from their own GP and will obtain the prescribed medication
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59 March 8th, 2019, version 3
60 For peer review only - <http://bmjopen.bmjjournals.org/site/about/guidelines.xhtml>

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3 209 from the child's own pharmacy.
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5 210 Besides the use of corticosteroids, all children (control and intervention group) will
6
7 211 always be advised to use indifferent therapy with a standard emollient (i.e.
8
9 212 'cetomacrogol'). The advice is to use the emollients daily.

10
11 213 *Patient and Public Involvement*
12

13 214 The recommendations in the Dutch guideline are based on scientific research. It appears,
14 however, that research to support recommendations is sometimes lacking or inadequate. The
15 Dutch guideline states as a knowledge gap ('lacunebak') that it is not clear which treatment
16 strategy, mild or potent CS, is best when treating a flare-up of AD. (12) This stated knowledge
17 gap resulted in the research question of our study.

18 218
19 219 The outcome measures are based on the recommendations stated by the HOME-initiative.
20
220 During the development of the core outcome set and its measurement tools by this initiative,
21 patients have been intensively involved.

221 222 The burden of the intervention is similar to the control group, both groups will use cream.
223 Therefore, the burden of the intervention was not specifically discussed with patients.

224 Study participants will be informed about the results by a simplified summary send by email.

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226 **Outcomes**

227 **Primary outcome measure**

228 The primary outcome will be change in disease severity over 24-weeks follow-up in the
229 trial, as measured by the average score of the Patient-Oriented Eczema Measure
230 (POEM). POEM is a patient-reported outcome based on symptoms over the previous
231 week, which can be self-completed by the child's parent or the child. POEM is a
232 validated questionnaire and has been recommended by the Harmonizing Outcome for
233 Eczema (HOME) initiative as the preferred instrument to capture patient-reported
234 symptoms in eczema trials.(20) The POEM score is collected weekly in the trial part
235 over 24 weeks and, to measure long-term control, the difference between the two
236 treatment groups in the average POEM scores will be measured over these 24 weeks.

237

238 **Secondary outcome measures**

239 The Eczema Area and Severity Index (EASI) will be used as objective measurement of
240 the AD. The EASI has been identified by the HOME initiative as the core outcome
241 measurement instrument to evaluate clinical signs of AD in all future trials investigating
242 interventions for AD. (21) The EASI is scored by a physician and rates both the intensity
243 and extent of AD signs. The EASI will be used as secondary outcome in both the trial
244 and the cohort study. The EASI score is collected at baseline, and at weeks 1, 4 and 24
245 of the trial, and at baseline, and at weeks 26 and 52 in the cohort study. See table 1 for
246 an overview of observations made during the study.

247 Other secondary outcomes in the trial part include: i) changes in disease severity after 1
248 week and 4 weeks using POEM, ii) QoL using the Infants' Dermatitis Quality of Life
249 Index (IDQOL) or Children's Dermatology Life Quality Index (CDLQI) (depending on
250 age), iii) medication compliance (determined as a POEM >8 and use of TCS during that
251 week), iv) local side-effects (painful application, telangiectasia, atrophy,
252 hypopigmentation, and striae), v) time to recovery (i.e. time till start weaning-off
253 treatment), vi) frequency of flare-ups, vii) medication use (subjective and objective), viii)
254 patient global assessment and investigator global assessment (both on a 6-point scale;
255 clear, almost clear, mild, moderate, severe, very severe), ix) itch intensity score (the
256 numeric rating scale-11 is ranging from 0, no itch to 10, worst itch imaginable), and x)

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3 257 healthcare use (i.e. telephone contact with GP, consultation at the general practice, or
4 258 referral to secondary care).
5
6 259 The QoL questionnaires are the IDQOL and CDLQI: both are validated and widely used
7 260 in dermatology as a QoL scale for children aged ≤4 years and aged 4-16 years,
8 261 respectively. (22, 23). The use of medication will be registered by weighing the tube of
9 262 TCS after 1 week, 4 weeks and 24 weeks in the trial. Furthermore, in the weekly
10 263 questionnaire, the children will register the amount of days that TCS and neutral
11 264 ointment were used in the previous week.
12
13 265 The aim of the observational cohort is to determine the frequency and determinants of
14 266 flare-ups of AD after 1-year follow-up.
15
16 267 Secondary outcomes concerning the cohort includes disease severity at inclusion, and
17 268 at 26 weeks and 52 weeks follow-up using POEM and EASI, QoL, frequency of flare-
18 269 ups, medication use, and healthcare use.
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272 Table 1. Schedule of observations made during the study.

| Outcomes collected | Cohort | | | Weekly for 52 weeks | Trial | | Weekly for 24 weeks |
|-----------------------------------------------------------------------------------------------------------------------|----------|---------|---------|---------------------|----------|--------|---------------------|
| | Baseline | Week 26 | Week 52 | | Baseline | Week 1 | |
| Proxy-reported/patient reported outcomes | | | | | | | |
| Eczema severity over past week (POEM) | V | | | V | V | | V |
| Eczema-related quality of life (IDQOL/CDLQI) | V | V | V | V | V | V | V |
| Flare-up | | | | V | | | V |
| Amount of days emollients used in past week | | | | V | | | V |
| Amount of days TCS used in past week | | | | V | | | V |
| Use of medication other than TCS in past week | | | | V | | | V |
| Adverse effects from treatment in past week | | | | V | | | V |
| Doctor's visits in past week | | | | V | | | V |
| Objective reported outcomes | | | | | | | |
| Three Item Severity score | | | | | V | | |
| Eczema area and severity (EASI) | V | V | V | | V | | V |
| Weigth | | | | | V | | V |
| Length | | | | | V | | V |
| Head circumference | | | | | V | | V |
| Weigh medication | | | | | V | | V |
| 273 | | | | | | | |
| 274 POEM= Patient-Oriented Eczema Measure, EASI= Eczema Area and Severity Index, IDQOL= Children's Dermatitis Quality | | | | | | | |
| 275 of Life Index , CDLQI= Children's Dermatology Life Quality Index ,TCS= Topical corticosteroid, PG= Patient global | | | | | | | |
| 276 assessment, IGA= Investigator global assessment | | | | | | | |

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3 277 **Sample size**
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5 278 In this study, we based our sample size calculation on the minimal clinically important
6 difference (MCID) of the POEM in young children with eczema as determined by Gaunt
7 at al.(24) The MCID is the smallest change in an outcome measure that represents a
8 clinically relevant outcome. A treatment effect of 3.0 POEM points was considered
9 clinically relevant. We used a mean of 128.8 (SD of 5.9) as presented in trials with a
10 similar population (i.e. primary care patients) on baseline POEM characteristics. (24)
11
12 284 Taking these numbers into account, with a power of 80% and $\alpha=0.05$ (2-sided) we need
13 61 children per trial group. Assuming a dropout rate of 15% during the study, 72
14 children per treatment arm are required.
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23 288 **Recruitment**
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25 289 Based on Dutch GP data and an expected patient participation of 50%, per participating
26 GP we expect to include 7 children per year for the cohort, and 4 in the trial (based on
27 flare-ups). (2) Therefore, we expect to need about 36 participating GPs. First, we will
28 collaborate with our academic network named PRIMEUR. The academic PRIMEUR
29 network includes 13 centers with about 97 participating GPs and about 160,000
30 patients. If the inclusion is behind expectations, more GPs will be invited to participate in
31 the study. Furthermore, if inclusion still remains behind expectations using the search
32 protocol (e.g. consultation, or repeated prescription in the previous 12 months) we will
33 expand the search period from 12 to 24 months.
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40 298 Children will be recruited from general practices. When a GP decides to participate, the
41 GP will perform a search in their information system to identify all possible eligible
42 children. Invitation letters to participate (in the name of the GP) will be sent to the
43 parent/carer of the children.
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46 302 Children are asked to respond using a response card or response e-mail, irrespective of
47 whether or not they are willing to participate. These responses are sent to the
48 coordinating researcher of the department of General Practice, Erasmus Medical Center
49 Rotterdam.
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52 306 After receiving a positive response from the child, the research assistant will have
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3 307 telephone contact with the child (this can be with the parents if the child is aged ≤ 12
4 years, or the children themselves). During this telephone contact, additional information
5 on the study and study procedures will be explained. Based on the telephone contact, if
6 the child is eligible and is still interested in participating, the patient information letter
7 (PIF) will be sent by mail. Afterwards, if the child is willing to participate, the informed
8 consent will be signed by the parents (if the child is aged ≤ 16) or the child (when aged
9 ≥12 years) and sent to the department of General Practice.
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15 314 After receiving the signed PIF, the research assistant will contact the general practice of
16 the child to inform them about the child's participation. The GP practice will contact the
17 parents of the child to arrange a consultation. During this first consult with the physician
18 assistant, the baseline EASI will be obtained.
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24 319 **Assignment of interventions**
25 320 When the AD flares up, the child (or the child's parents) has to make an appointment by
26 the GP. The definition of a flare-up is the need to intensify topical treatment from the
27 patient's and/or parents' point of view
28
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30 323 If the child has a flare-up of AD and is eligible for inclusion in the trial, the child will be
31 randomly allocated to one of the two groups by the physician assistant of their own GP,
32 using the data management system (Research manager). The randomization list will be
33 computer-generated and unknown to the investigators.
34
35

36 327 Children will be stratified by TIS score (i.e. TIS score 3, 4 and 5) to ensure equal
37 distribution of the severity of AD between the intervention and control group. Random
38 permuted blocks of two will be generated. The GP will prescribe the medication of
39 randomization.
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44 332 **Data collection and methods**
45 333 Data collection of the patient-reported outcomes and the objective reported outcomes
46 will be carried out using online case report forms. Children (or the child's parents) will
47 receive a reminder by email if questionnaires are not filled in after a standardized
48 interval of three days. If questionnaires are not filled in at key time points, participants
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3 337 will receive a telephone reminder. Children will receive a small gift after completing the
4 cohort or trial follow-up. The weekly questionnaires include a question on who
5 completed the questionnaire, the child, the parent or together. We can therefore take
6 into account by whom the questionnaire has been completed in our analysis. If patients
7 are 16 years or older, they will complete the questionnaires themselves. Children under
8 16 are free in their choice to complete the questionnaire themselves or together with /
9 by a parent. The physician assistants will received additional training in the
10 pathophysiology and treatment of AD and in scoring the EASI.
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19 345
20 346 **Data management**
21 347 Data will be handled confidentially and anonymously. A child's identification code is
22 348 used to link the data to the child; a unique code is randomly generated for each
23 349 individual. The principal investigator safeguards the key to the code.
24
25 350 The software program Research Manager will be used for the online questionnaires and
26 351 the childrens' personal data, respectively.
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32 353 **Statistical methods**
33 354 All analyses of the primary study parameters will be performed according to the
34 intention-to-treat principle (ITT), i.e. irrespective of compliance. Those who perform the
35 analyses will be kept blind regarding which group has received what kind of treatment.
36
37
38 357 Secondary, a per-protocol analysis, excluding children in whom major violations of the
39 protocol have occurred, will also be performed. Major protocol violations are: withdrawal
40 from study or loss to follow-up, and medication compliance <75%.
41
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44 360 In case major events occur during the study period that necessitate withdrawal from
45 study, or loss-to-follow-up/dropout for other reasons, weekly diary card data will be
46 evaluated up to the week of such dropout. However, children are requested to agree
47 with further follow-up according to the study protocol (e.g. weekly questionnaires).
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50 364 Medication compliance <75%, (also called non-compliance) is determined as a POEM
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52 365 >8 and no use of TCS during that week; the compliance is determined per week.
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3 366 For the primary outcome, statistical comparison between the treatment groups will be
4 done using analysis of covariance (ANCOVA) including the covariates: baseline
5 symptom score, age, and gender. Treatment effects will be tested two-sided with a
6 significance level of 5%.
7
8 370 For the main study parameter, it is essential that the weekly diaries are filled in
9 adequately. However, in case of missing data, these will be imputed using multiple
10 imputation; this is considered the most appropriate way of dealing with missing data.
11
12 373 (25) Missing values of the POEM will be imputed 10 times using the multivariate
13 imputation by chained equations (MICE) logarithm (R-Project). The imputation model
14 included sex, age, type of medication used and frequency of application, and the
15 outcome measure POEM.
16
17 377 Secondary outcomes of the trial, statistical comparison between the treatment groups
18 for changes in disease severity, and QoL after 1 week and 4 weeks, will be performed
19 using ANCOVA, including the covariates baseline symptom score, age and gender. The
20 other secondary outcomes (i.e. local side-effects, systemic side-effects, compliance,
21 frequency of flare-ups, medication use and healthcare use) will be analyzed with linear
22 or logistic regression when appropriate. For the time to recovery, Cox regression
23 analyses will be performed.
24
25 384 To explore differences in patient and disease characteristics in the two treatment arms,
26 and to determine which factors are related to compliance to the two treatment
27 strategies, backward logistic regression will be used.
28
29 387 Patient characteristics to be examined are: age, sex, age at presentation of AD, history
30 of atopy (i.e. asthma, allergic rhinitis, food allergy and anaphylaxis), use of other CS (i.e.
31 nasal, inhaled, oral), and QoL (IDQoL, CDLQI). Disease characteristics are disease
32 severity (POEM and EASI), duration of AD, location of AD (i.e. head and neck, upper
33 limbs, lower limbs and trunk, all extracted from EASI) and previous medical care (i.e. no
34 previous treatment, GP only, GP and secondary care).
35
36 393 To explore which factors are related to compliance to the two treatment strategies,
37 backward logistic regression will be used. The factors to be explored are treatment arm,
38 age, sex, age at presentation of AD, disease severity (POEM and EASI), duration of
39 AD, use of other CS (i.e. nasal, inhaled, oral), and QoL (IDQoL, CDLQI).

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5 398 The secondary outcomes for the cohort will be analyzed with descriptive statistics (i.e.
6 disease severity, frequency of flare-ups, medication use, healthcare use, QoL).
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8 400 Analyses to determine what the determinants of flare-ups of AD are after 1-year follow-
9 up will be performed with logistic regression analyses.
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13 403 **Ethics and dissemination**
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15 404 The study protocol is approved by the Medical Ethics Committee (MEC) of the Erasmus
16 Medical Center Rotterdam, the Netherlands (MEC-2017-328).
17
18 406 Amendments are changes made to the research protocol after a favorable opinion from
19 the accredited MEC. All substantial amendments will be notified to the MEC and to the
20 competent authority.
21
22 408
23
24 409 The results of the study will be published in international peer-reviewed journals and
25 presented at (inter)national conferences. We aim to publish several peer-reviewed
26 publications on the best treatment strategy in children with AD related to patient-
27 oriented outcomes, healthcare consumption, and side-effects. The results of this study
28 may be implemented into clinical practice and/or can be used for the next update of the
29 Dutch guideline on AD for GPs.
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36 416 **Safety reporting**
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38 417 In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the
39 study if there is sufficient ground that continuation of the study will jeopardise subject
40 health or safety. The sponsor will notify the accredited METC without undue delay of a
41 temporary halt including the reason for such an action. The study will be suspended
42 pending a further positive decision by the accredited METC. The investigator will take
43 care that all subjects are kept informed.
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50 424 **Monitoring**
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52 425 Due to the characteristics of this study it is not necessary to install a Data Safety
53 Monitoring Board. Nevertheless, the study will be monitored as described in the ICH-
54 GCP Guidelines (chapter 5.18). The department of General Practice has developed a
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59 March 8th, 2019, version 3
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3 428 monitoring plan and monitoring checklist (based on the ICH-GCP Guidelines) which will
4 429 be used in this study. A senior researcher (project leader) will be designated as monitor.
5 430 This senior researcher is not related to the current project and is part of another
6 431 research discipline within the department. At various moments in the study (not known
7 432 to the researcher in front) an appointment will be made with the researcher and
8 433 projectleader of the current project to monitor the study by making use of the checklist
9 434 of the department of general practice.
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18 436 **Adverse events**
19 437 All (serious) adverse events and suspected unexpected serious adverse reactions
20 438 reported spontaneously by the subject or observed by the investigator or the staff will be
21 439 recorded.
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27 441 **Discussion**
28 442 This will be the first study to investigate the effectiveness of treatment with TCS class I
29 443 vs class III on long-term control over 6-months follow-up of children in primary care with
30 444 AD.
31
32 445 We chose an observational cohort design with an embedded pragmatic randomized
33 446 open-label trial, as it might be difficult to randomize children in primary care at the
34 447 moment they present with a flare-up. The observational cohort gives the opportunity to
35 448 follow the course of AD in children in primary care with regard to the frequency and
36 449 determinants of flare-ups, and the burden of disease. As primary outcome, we chose a
37 450 clinical outcome relevant to patients. In AD, the appearance of the skin does not always
38 451 closely reflect the subjective symptoms, i.e. when the latter causes a major impact on
39 452 the child and family. (9, 10) Therefore, it was particularly important to design a trial with
40 453 a validated participant-reported primary outcome.
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48 454 The structure of regular home visits will probably artificially improve treatment
49 455 adherence. It is generally known that treatment adherence is highest immediately after
50 456 seeing a doctor. (26)Both treatment arms will receive home visits, so this effect will be
51 457 equally spread. The home visits will influence the generalizability of the results.
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55 458 However, it is crucial for several outcome measures to visit the patients. We kept the
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frequency of home visits to a minimum, balancing the unwanted effect of better treatment adherence and gathering important information on study outcomes.

A limitation of the study is the open-label design. Since participants know which treatment arm they will be assigned to, they cannot be blinded to the intervention. Also, because the GP must be able to adjust the treatment strategy or refer the child if required, the GP cannot be blinded. The research assistants will also be aware of the medication use of the child, as they have to register and weigh the medication.

Given that our primary outcome is patient-reported, the additional costs for blinding researchers to collect the objective data (i.e. EASI) did not seem justifiable.

Concerns have been reported about the safety of TCS application in children with regard to incorrect application. (27) Potential local side-effects of TCS are painful application, telangiectasia, atrophy, hypopigmentation, and striae. However, there is a lack of evidence from good quality research concerning these local side-effects of TCS. (28) Nevertheless, in a study on children with AD with a follow-up of 18 weeks, no difference was found in skin atrophy in children using class-III TCS for 3 days per week vs children using class I TCS. (16) Potential systemic effects of TCS may include suppression of the HPA axis, and osteoporosis, glaucoma, cataract, and growth reduction. Although there is lack of evidence about these potential systemic side-effects, it is reported that topical TCS has little to no effect on the HPA axis, osteoporosis and growth reduction. (12, 14, 15, 29) In addition, the treatment scheme for the class III TCS is within the recommended dosage of the Dutch guideline on AD. (12) Additionally, we want to include children of all ages with atopic dermatitis on most widespread areas. Therefore, we chose a strong topical corticosteroid with the most favorable profile, this is found in fluticasone propionate 0.05% or 0.005% since it has a relatively short half-life as compared to the class III TCS that is recommended by the Dutch guideline (i.e. betamethasone). (12)

In this way, we aim to further reduce the already low risk of potential (systemic) side-effects; therefore, we believe that it is safe to use a class III TCS according to the previously described treatment scheme.

Experience from dermatologists indicate that starting with a high-dose TCS leads to a faster and better result as compared to starting with a low-dose TCS. However, most

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3 490 children with AD are treated by a GP (only about 1% is referred to secondary care) and
4 491 have a milder form of AD as compared to patients treated by a dermatologist. (2)
5 492 Whether the effects of initial treatment with a potent TCS as experienced in a specialist
6 493 setting can be transferred to treatment in primary care is unknown. Since the present
7 494 study will focus on these gaps, it will hopefully make an important contribution to
8 495 knowledge with respect to the use of local corticosteroids in children with AD treated in
9 496 general practice.
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19 498 **Figure legend**
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21 499 Figure 1: GP= General practitioner, EASI= Eczema Area and Severity Index, POEM=
22 500 Patient-Oriented Eczema Measure, AD= atopic dermatitis, TCS= Topical corticosteroid,
23 501 PGA= Patient global assessment
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505 REFERENCES

- 506
507
508 1. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric
509 population. *Pediatrics* 2008;122(4):812-824.
510 2. JCC Braspenning FS, RPTM Grol (redactie). Tweede Nationale Studie naar ziekten en
511 verrichtingen in de huisartspraktijk. Kwaliteit huisartsenzorg belicht. Utrecht/Nijmegen: NIVEL/WOK;
512 2004.
513 3. Watson W, Kapur S. Atopic dermatitis. *Allergy Asthma Clin Immunol* 2011;7 Suppl 1:S4.
514 4. Larsen FS, Hanifin JM. Epidemiology of atopic dermatitis. *Immunology and Allergy Clinics of*
515 *North America* 2002;22(1):1-24.
516 5. Pols DHJ, Nielen MMJ, Korevaar JC, Bindels PJE, Bohnen AM. Reliably estimating prevalences of
517 atopic children: an epidemiological study in an extensive and representative primary care database. *NPJ*
518 *Prim Care Respir Med* 2017;27(1):23.
519 6. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358(14):1483-1494.
520 7. Tollefson MM, Bruckner AL, Section On D. Atopic dermatitis: skin-directed management.
521 *Pediatrics* 2014;134(6):e1735-1744.
522 8. Chang YS, Chou YT, Lee JH, Lee PL, Dai YS, Sun C, et al. Atopic dermatitis, melatonin, and sleep
523 disturbance. *Pediatrics* 2014;134(2):e397-405.
524 9. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial
525 cost. *Arch Dis Child* 1997;76(2):159-162.
526 10. Barbeau M, Bpharm HL. Burden of Atopic dermatitis in Canada. *Int J Dermatol* 2006;45(1):31-36.
527 11. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health*
528 *Technol Assess* 2000;4(37):1-191.
529 12. Dirven-Meijer PC DKC, Nonneman MGM, Van Sleeuwen D, De Witt-de Jong AWF, Burgers JS,
530 Opstelten W, De Vries CJH. NHG-Standaard Eczeem. *Huisarts wet* 2014;57(5):240-252.
531 13. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term
532 safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic
533 dermatitis. *BMC Pediatr* 2016;16:75.
534 14. van Velsen SG, Knol MJ, van Eijk RL, de Vroede MA, de Wit TC, Lam MG, et al. Bone mineral
535 density in children with moderate to severe atopic dermatitis. *J Am Acad Dermatol* 2010;63(5):824-831.
536 15. Thomas MW, Panter AT, Morrell DS. Corticosteroids' effect on the height of atopic dermatitis
537 patients: a controlled questionnaire study. *Pediatr Dermatol* 2009;26(5):524-528.
538 16. Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S, et al. Randomised controlled trial of
539 short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children
540 with mild or moderate atopic eczema. *Bmj* 2002;324(7340):768.
541 17. Kirkup ME, Birchall NM, Weinberg EG, Helm K, Kennedy CT. Acute and maintenance treatment
542 of atopic dermatitis in children - two comparative studies with fluticasone propionate (0.05%) cream. *J*
543 *Dermatolog Treat* 2003;14(3):141-148.
544 18. Vernon HJ, Lane AT, Weston W. Comparison of mometasone furoate 0.1% cream and
545 hydrocortisone 1.0% cream in the treatment of childhood atopic dermatitis. *J Am Acad Dermatol*
546 1991;24(4):603-607.
547 19. (SIGN) SIGN. Management of atopic eczema in primary care. Edinburgh: SIGN. SIGN publication
548 no. 125 March 2011(Available from URL: <http://www.sign.ac.uk>).
549 20. Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-
550 Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a
551 Harmonising Outcome Measures for Eczema (HOME) statement. *Br J Dermatol* 2017;176(4):979-984.

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3 552 21. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome
4 Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin
5 Immunol* 2014;134(4):800-807.
6 555 22. Salek MS, Jung S, Brincat-Ruffini LA, MacFarlane L, Lewis-Jones MS, Basra MK, et al. Clinical
7 experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-
8 557 2012. *Br J Dermatol* 2013;169(4):734-759.
9 558 23. Basra MK, Gada V, Ungaro S, Finlay AY, Salek SM. Infants' Dermatitis Quality of Life Index: a
10 559 decade of experience of validation and clinical application. *Br J Dermatol* 2013;169(4):760-768.
11 560 24. Gaunt DM, Metcalfe C, Ridd M. The Patient-Oriented Eczema Measure in young children:
12 561 responsiveness and minimal clinically important difference. *Allergy* 2016;71(11):1620-1625.
13 562 25. Groenwold RH, Donders AR, Roes KC, Harrell FE, Jr., Moons KG. Dealing with missing outcome
14 563 data in randomized trials and observational studies. *Am J Epidemiol* 2012;175(3):210-217.
15 564 26. Feldman SR, Camacho FT, Krejci-Manwaring J, Carroll CL, Balkrishnan R. Adherence to topical
16 565 therapy increases around the time of office visits. *J Am Acad Dermatol* 2007;57(1):81-83.
17 566 27. Aubert-Wastiaux H, Moret L, Le Rhun A, Fontenoy AM, Nguyen JM, Leux C, et al. Topical
18 567 corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. *Br J Dermatol*
19 568 2011;165(4):808-814.
20 569 28. Callen J, Chamlin S, Eichenfield LF, Ellis C, Girardi M, Goldfarb M, et al. A systematic review of
21 570 the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007;156(2):203-221.
22 571 29. Friedlander SF, Hebert AA, Allen DB, Fluticasone Pediatrics Safety Study G. Safety of fluticasone
23 572 propionate cream 0.05% for the treatment of severe and extensive atopic dermatitis in children as
24 573 young as 3 months. *J Am Acad Dermatol* 2002;46(3):387-393.
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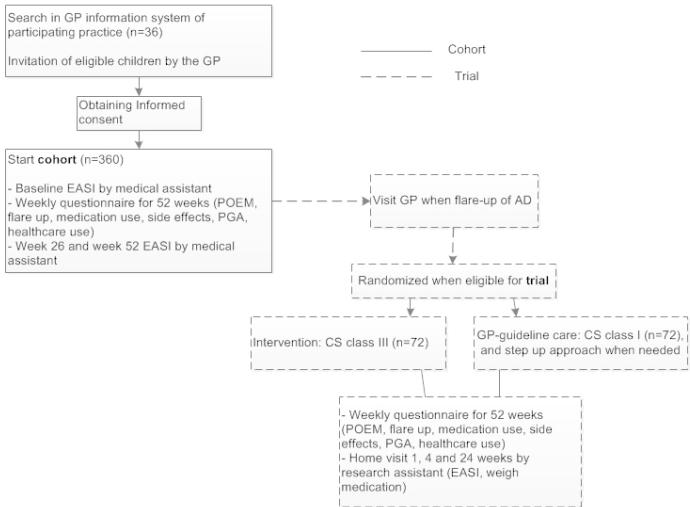


Figure 1. Flow chart of the study.

90x90mm (300 x 300 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|-----------------------------------|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | 3 | Date and version identifier | footer |
| Funding | 4 | Sources and types of financial, material, and other support | 1 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |

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Introduction

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|--------------------------|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4 and 5 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 5 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, cluster, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 and 6 |

Methods: Participants, interventions, and outcomes

| | | | |
|----------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of study sites where data will be collected. Reference to where list of study sites can be obtained | 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | n/a |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 9 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variables (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8 and 9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | figure 1 |

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| | | | | |
|----|---------------------------------------------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9 |
| 2 | | | | |
| 3 | Methods: Assignment of interventions (for controlled trials) | | | |
| 4 | Allocation: | | | |
| 5 | | | | |
| 6 | Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 11 |
| 7 | | | | |
| 8 | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 11 |
| 9 | | | | |
| 10 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 11 |
| 11 | | | | |
| 12 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| 13 | | | | |
| 14 | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 12 |
| 15 | | | | |
| 16 | Methods: Data collection, management, and analysis | | | |
| 17 | | | | |
| 18 | Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11 and 12 |
| 19 | | | | |
| 20 | | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | n/a |
| 21 | | | | |

| | | | | |
|----|---------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1 | Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 12 |
| 2 | Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 12 and 13 |
| 3 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13 |
| 4 | | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised), and any statistical methods to handle missing data (eg, multiple imputation) | 13 |
| 5 | Methods: Monitoring | | | |
| 6 | Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and references to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 14 |
| 7 | | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| 8 | Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 14 |
| 9 | Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
| 10 | Ethics and dissemination | | | |
| 11 | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 13 |
| 12 | Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 13 |

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|----|-------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| 1 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32) | 10 |
| 2 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| 3 | | | | |
| 4 | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 12 |
| 5 | | | | |
| 6 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 1 |
| 7 | | | | |
| 8 | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 12 |
| 9 | | | | |
| 10 | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| 11 | | | | |
| 12 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 14 |
| 13 | | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| 14 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level datasets, and statistical code | n/a |
| 15 | | | | |
| 16 | Appendices | | | |
| 17 | | | | |
| 18 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorized surrogates | Figure 2 |
| 19 | | | | |
| 20 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |
| 21 | | | | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.