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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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Authors' contributions

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

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Competing interests

There are no competing interests for any authors.

Trial registration

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

Abstract

Introduction

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

Methods and Analysis

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

Ethics and Dissemination

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

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 d4privation.(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

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

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

Objectives

To determine whether initial treatment with a potent TCS is more effective than a mild TCS in the treatment of children with a moderate flare-up of AD in primary care in the short (i.e. 1 week and 4 weeks of follow-up) and long-term (i.e. 6 months follow-up) control of the disease.

In the observational cohort, the aim is to determine the frequency and determinants of flare-ups of AD. Furthermore, we will explore the burden of AD by measuring severity, medication use, healthcare use and quality of life (QoL) during 1-year follow-up.

Study design

The Rotterdam Eczema study is an observational cohort study with an embedded

pragmatic randomized open-label superiority trial with two groups and a patient-reported primary outcome of long-term control.

Methods; participants, interventions and outcomes

Healthcare system

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

Study setting

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

Eligibility criteria

To be eligible to participate in the cohort study, a child must meet all of the following criteria: aged between 12 weeks and 18 years, diagnosis of eczema (ICPC code S87 and S88 or prescription of topical treatment for eczema) plus confirmation of the diagnosis by the GP, a consultation or repeated prescription in the previous 12 months, and informed consent. Exclusion criteria for the cohort study are: as determined by the GP (e.g. family problems), currently under treatment with a dermatologist, contra-indications for the study medication, language barrier, or no access to internet (necessary to fill in weekly online questionnaire).

The inclusion criteria for the trial part of the study are: participation in the cohort, flare-up (i.e. need to intensify topical treatment) from the child's and/or parents' point of view, a Three Item Severity (TIS) score from ≥3 to <6. Exclusion criteria for the trial part are: use of TCS in the 2 weeks before inclusion in the trial, AD on eyelid(s), >50% of body affected by AD, other skin disorders hampering proper assessment of eczema,

pregnancy and or breastfeeding, or untreated skin infections (bacterial, viral, fungal or parasitic).

Interventions

Eligible children will participate in the trial part if they have a flare-up of AD. They will be randomized to either the **intervention group** or to the GP guideline group (**control group**). Those allocated to the intervention group will receive a potent TCS class III once daily to start with at each flare-up during the follow-up period of the trial. If children are aged >2 years, they will follow a predefined weaning-off scheme (i.e. reduction of frequency) when their symptoms have improved. If children are aged <2 years, they will be reassessed 7by the GP after 1-2 weeks. When AD is improved but still needs treatment, children will be treated according to the Dutch GP guideline (i.e. switch to a less potent TCS).

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

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

Besides the use of corticosteroids, all children (control and intervention group) will always be advised to use indifferent therapy with a standard emollient (i.e. 'cetomacrogol'). The advice is to use the emollients daily.

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;

clear, almost clear, mild, moderate, severe, very severe), ix) itch intensity score (the numeric rating scale-11 is ranging from 0, no itch to 10, worst itch imaginable), and x) healthcare use (i.e. telephone contact with GP, consultation at the general practice, or referral to secondary care).

The QoL questionnaires are the IDQOL and CDLQI: both are validated and widely used in dermatology as a QoL scale for children aged ≤4 years and aged 4-16 years, respectively. (22, 23). The use of medication will be registered by weighing the tube of TCS after 1 week, 4 weeks and 24 weeks in the trial. Furthermore, in the weekly questionnaire, the children will register the amount of days that TCS and neutral ointment were used in the previous week.

The aim of the observational cohort is to determine the frequency and determinants of flare-ups of AD after 1-year follow-up.

Secondary outcomes concerning the cohort includes disease severity at inclusion, and at 26 weeks and 52 weeks follow-up using POEM and EASI, QoL, frequency of flare-ups, medication use, and healthcare use.

Table 1. Schedule of observations made during the study.

Sample size

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

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 patie1nt'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 received 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.

Safety reporting

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

Monitoring

Due to the characteristics of this study it is not necessary to install a Data Safety Monitoring Board. Nevertheless, the study will be monitored as described in the ICH-GCP Guidelines (chapter 5.18). The department of General Practice has developed a monitoring plan and monitoring checklist (based on the ICH-GCP Guidelines) which will be used in this study. A senior researcher (project leader) will be designated as monitor. This senior researcher is not related to the current project and is part of another research discipline within the department. At various moments in the study (not known to the researcher in front) an appointment will be made with the researcher and projectleader of the current project to monitor the study by making use of the checklist of the department of general practice.

Adverse events

All (serious) adverse events and suspected unexpected serious adverse reactions reported spontaneously by the subject or observed by the investigator or the staff will be recorded.

Discussion

This will be the first study to investigate the effectiveness of treatment with TCS class I vs class III on long-term control over 6-months follow-up of children in primary care with AD.

We chose an observational cohort design with an embedded pragmatic randomized

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

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 children with AD are treated by a GP (only about 1% is referred to secondary care) and have a milder form of AD as compared to patients treated by a dermatologist. (3) Whether the effects of initial treatment with a potent TCS as experienced in a specialist setting can be transferred to treatment in primary care is unknown. Since the present study will focus on these gaps, it will hopefully make an important contribution to knowledge with respect to the use of local corticosteroids in children with AD treated in general practice.

Figures legends

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

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,

Figure 2: PIF=Patient information file

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Figure 1. Flowchart of the study

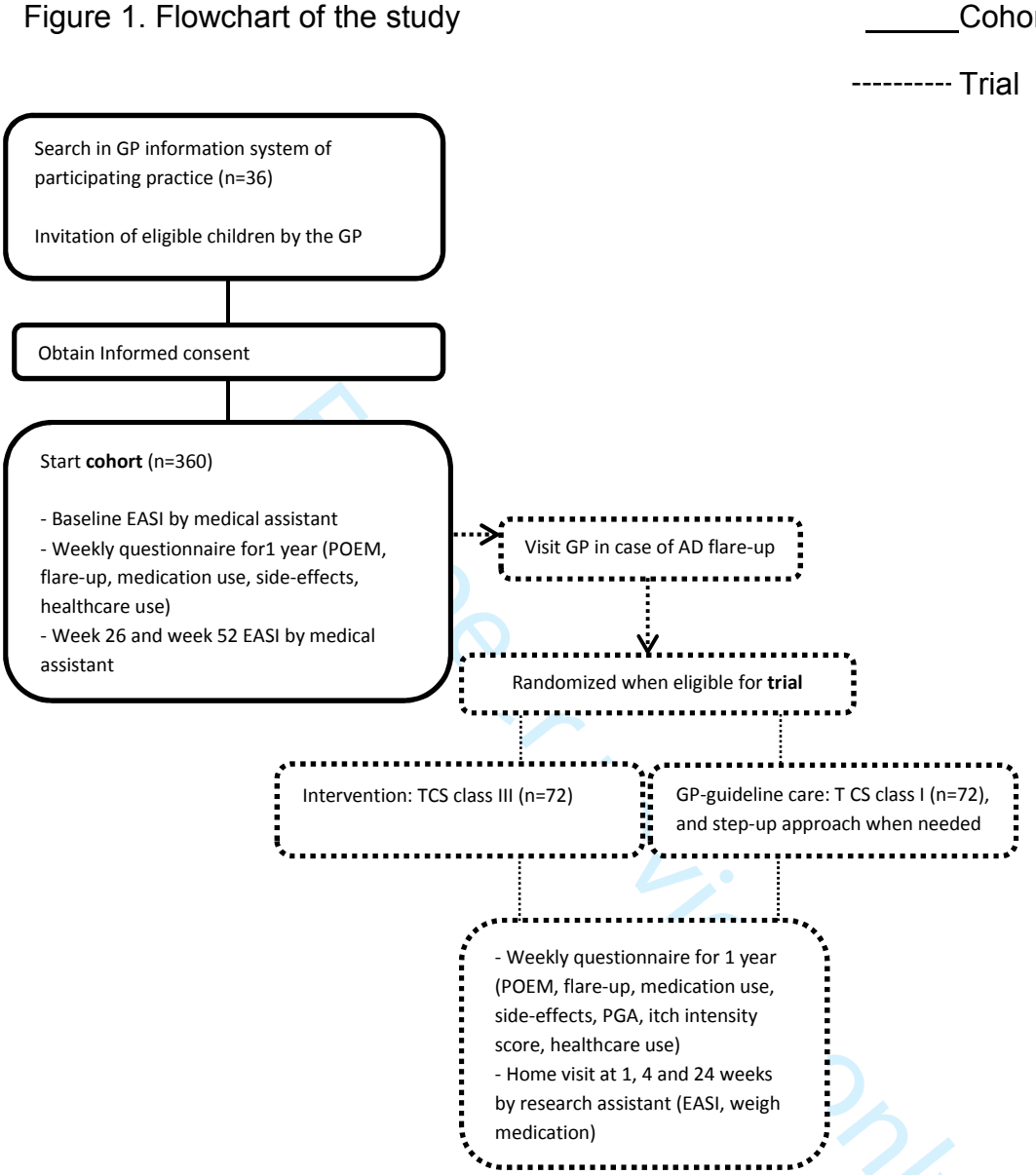


Table 1 Schedule of observations made during the study.

Outcomes collected	Cohort				Trial				
	Baseline	Week 26	Week 52	Weekly for 52 weeks	Baseline	Week 1	Week 4	Week 24	Weekly for 24 weeks
Proxy-reported/patient-reported outcomes									
• Eczema severity over past week (POEM)	√			√	√				√
• Eczema-related quality of life (IDQOL/CDLQI)	√	√	√		√	√	√	√	
• Flare up				√					√
• Amount of days emollients used in past week				√					√
• Itch intensity score									√
• Patient global assessment				√					√
• Amount of days TCS used in past week				√					√
• Use of medication other than TCS in past week				√					√
• Adverse effects from treatment in past week				√					√
• Physician visits in past week				√					√
Objective-reported outcomes									
• Three-Item Severity score					√				
• Eczema area and severity index (EASI)	√	√	√		√	√	√	√	
• Investigator global assessment					√	√	√	√	
• Weight						√	√	√	
• Height						√	√	√	
• Head circumference						√	√	√	
• Weigh medication						√	√	√	

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. Meedoen 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 meedoen 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 observatiedeel 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

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.

3. Welke medicijnen worden er gebruikt in dit onderzoek?

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: hydrocortisonacetaatcrème1%), klasse II (matig: triamcinolonacetonidecrème 0.1%) en klasse III crème (sterk: fluticasonpropionaatcrème 0.05%).

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

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?

Alle drie de gebruikte middelen zijn bekende middelen die al jaren op de markt zijn en gebruikt worden voor onder andere de behandeling van eczeem. De bijwerkingen van deze medicijnen zijn daarom goed bekend. De meest voorkomende bijwerkingen van corticosteroïdcrème zijn een dunne huid, kleine zichtbare bloedvaatjes, streperigheid van de huid (ook wel striae genoemd) en niet-wegdrukbare roodheid. Andere, minder vaak voorkomende bijwerkingen van de corticosteroïdcrèmes staan in bijlage D en in de bijsluiter. Als uw kind ernstige bijwerkingen krijgt die niet beschreven staan in de bijlage en bijsluiter moet u direct contact opnemen met uw huisarts. De bijwerkingen die uw kind heeft, moeten worden ingevuld in de wekelijkse online vragenlijst.

7. Wat zijn voor mijn zoon/dochter de nadelen?

Uw kind zal geen medicatie mogen gebruiken uit de andere groep dan ingedeeld, zonder eerst te overleggen met de huisarts. Daarnaast vragen wij u of uw kind wekelijks een korte online vragenlijst in te vullen.

Zoals elk geneesmiddel kunnen de geneesmiddelen die gebruikt worden in deze studie bijwerkingen veroorzaken, maar niet iedereen krijgt hiermee te maken.
Verder moet nog gemeld worden dat de medicatie niet gebruikt mag worden tijdens de zwangerschap. Het is dus heel belangrijk dat uw dochter niet zwanger is of wordt als zij mee gaat doen aan het onderzoek. Mocht uw dochter zwanger zijn, geef dit dan door aan de onderzoekers. Wij vragen haar dan te stoppen met het onderzoek.

8. Wat gebeurt er bij verzet van uw zoon of dochter bij deelname aan het onderzoek?

Het kan zijn dat uw zoon of dochter tijdens het onderzoek op de praktijk of de huisbezoeken zich verzet, denk hierbij aan sterke angst, verdriet of boosheid. De onderzoeker moet het onderzoek dan direct stoppen.

9. Kan ik mijn zoon/dochter tijdens het onderzoek nog terugtrekken?

Ja, de deelname van uw kind is volkomen vrijwillig. Hij of zij mag op ieder moment, zonder opgaaf van reden, stoppen met het onderzoek. Dit heeft geen enkel gevolg voor zijn of haar verdere behandeling. Meer informatie hierover vindt u in de Algemene Brochure.

10. Vergoeding voor mee doen

De studiemedicatie en behandeling van de huisarts voor het onderzoek kost u niets. U wordt niet betaald voor het meedoen aan dit onderzoek. Verder krijgt u een vergoeding voor uw (extra) reiskosten. Daarnaast krijgt uw kind na afronden van het onderzoek een kleinigheidje.

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.

16. Welke medisch-ethische toestemmingscommissie heeft dit onderzoek goedgekeurd?

De Medisch Ethische Toetsingscommissie van het Erasmus MC Rotterdam heeft dit onderzoek goedgekeurd. Meer informatie over de goedkeuring vindt u in de Algemene Brochure.

17. Ondertekening toestemmingsformulier

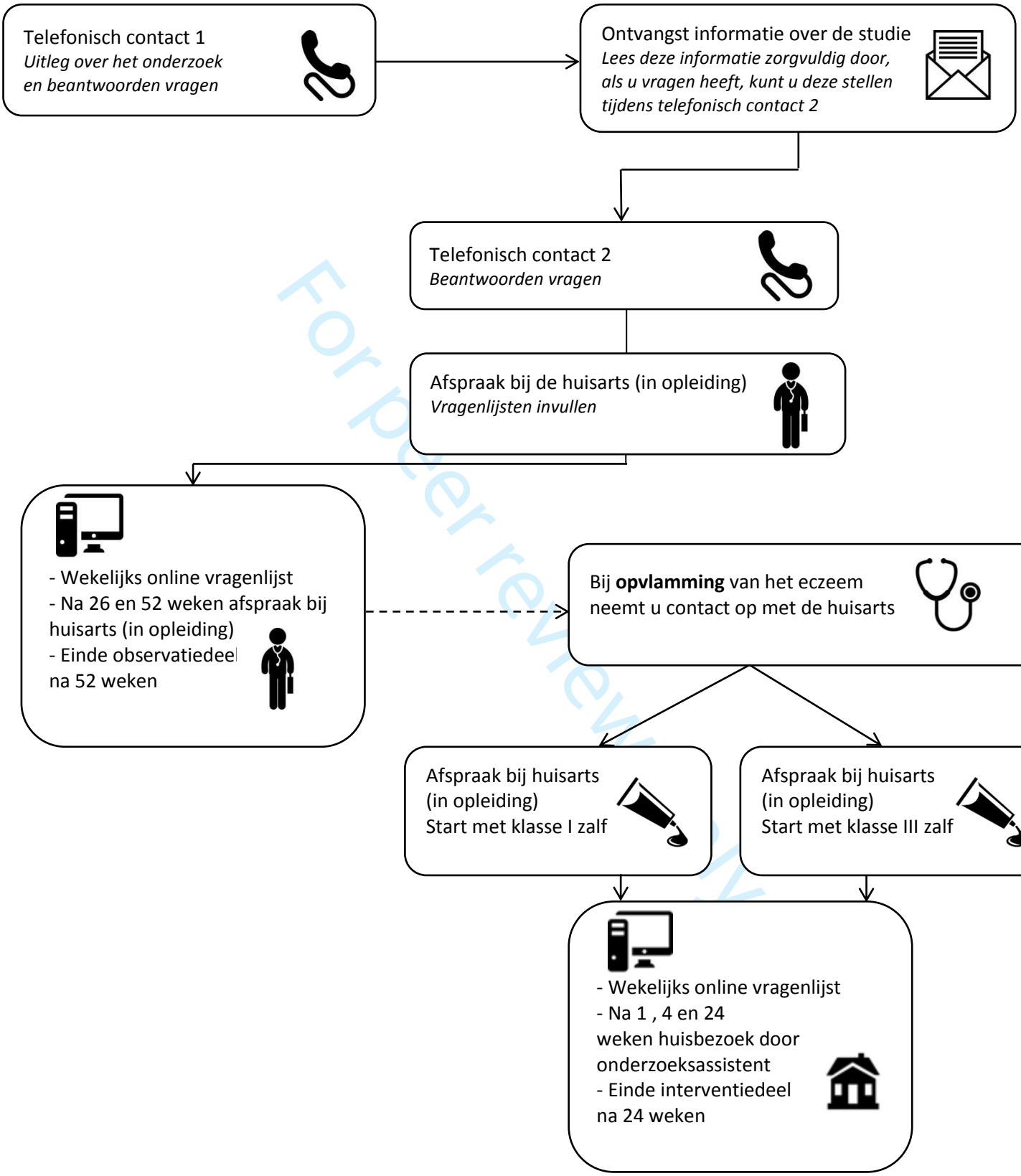
Wanneer u voldoende bedenktijd heeft gehad, wordt u gevraagd te beslissen over deelname aan dit onderzoek. Indien u toestemming geeft, zullen wij u vragen deze op de bijbehorende toestemmingsverklaring schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek.
Het handtekeningenblad wordt door uw behandelend arts bewaard. U krijgt een kopie of een tweede exemplaar van deze toestemmingsverklaring.
Als uw kind jonger is dan 16 jaar, ondertekenen de ouders die het gezag uitoefenen of de voogd dit formulier. Kinderen van 12 tot en met 15 jaar moeten daarnaast zelf een formulier ondertekenen.

Dank voor uw aandacht.

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

Bijlage A: Schematisch overzicht onderzoek



Bijlage B: Contactgegevens

U kunt voor verdere informatie over het onderzoek of over de te gebruiken medicatie terecht bij:

Mevrouw K.F. van Halewijn, onderzoeker
Afdeling Huisartsgeneeskunde Rotterdam
E-mail: k.vanhalewijn@erasmusmc.nl
Tel: 010-7032117

Ook uw huisarts is op de hoogte van dit onderzoek, als u vragen heeft, kunt u die ook aan hem of haar stellen.
Als u twijfelt over deelname kunt u een onafhankelijk arts raadplegen die zelf niet bij het onderzoek betrokken is, maar wel deskundig is op het gebied van dit onderzoek. Ook als u voor of tijdens het onderzoek vragen hebt die u liever niet aan de onderzoekers stelt, kunt u contact opnemen met de onafhankelijk arts:

Mevrouw A. Verwoerd, huisarts. Telefoonnummer: 010-7044194

Als u niet tevreden bent over het onderzoek of de behandeling kunt u terecht bij de onafhankelijke klachtencommissie van het Erasmus MC. De klachtencommissie is te bereiken onder telefoonnummer 010-4633198.

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)

Bijwerkingen op de rest van het lichaam:

Bijwerkingen op de rest van het lichaam (systemische bijwerkingen) ten gevolge van gebruik van corticosteroïdpreparaten komen zelden voor, maar kunnen ernstig zijn.

Remming van de bijnierschors kan vooral van betekenis zijn bij langdurig gebruik.

De kans op bijwerkingen op de rest van het lichaam is het grootst bij:

- toepassing waarbij de huid wordt afgesloten (afsluitend verband, plastic, huidplooien)
- toepassing op grote huidoppervlakken
- langdurige toepassing
- het gezicht, de behaarde huid en de huid van de geslachtsdelen zijn bijzonder gevoelig voor lokale effecten.
- toepassing bij kinderen (de dunne huid en het relatief grote huidoppervlak maken kinderen zeer gevoelig).

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

Triamcinolonacetonidecrème 0.1% (klasse II)

Zoals elk geneesmiddel kan triamcinolonacetonidecrème 0.1% 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 achtige) en blaarvorming en/of schilfering van de huid rondom de mond, met of zonder huidatrofie
- 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 (teleangiëctastieën), 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** voorkomen:

- overmatige haargroei (hypertrichosis)
- geelwitte speldenknopgrote knobbeltjes (colloid-milia)
- rood worden en toenemende afschilfering van de huid (erythrosis interfollicularis colli)
- overgevoeligheidsreacties op de plaats van insmeren met roodheid van de huid en jeuk (contactallergie)
- bruinrode huidknobbeltjes (granuloma gluteale).
- een verhoging van de oogboldruk en vergroting van de kans op grijze staar (cataract).

Bijwerkingen op de rest van het lichaam:

Bijwerkingen op de rest van het lichaam (systemische bijwerkingen) ten gevolge van gebruik van corticosteroïdpreparaten komen zelden voor, maar kunnen ernstig zijn.

Remming van de bijnierschors kan vooral van betekenis zijn bij langdurig gebruik.

De kans op bijwerkingen op de rest van het lichaam is het grootst bij:

- toepassing waarbij de huid wordt afgesloten (afsluitend verband, plastic, huidplooien)
- toepassing op grote huidoppervlakken
- langdurige toepassing
- het gezicht, de behaarde huid en de huid van de geslachtsdelen zijn bijzonder gevoelig voor lokale effecten.
- toepassing bij kinderen (de dunne huid en het relatief grote huidoppervlak maken kinderen zeer gevoelig).

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.

Fluticasonpropionaatcrème 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 galbulten (urticaria)
- infectie die kan optreden bij mensen met verminderde weerstand (opportunistische infectie)
- dunnere huid (atrofie)
- streepvorming van de huid (striae)
- ontkleuring van de huid (hypopigmentatie)
- overmatige haargroei in bepaald gebied (hypertrichose)

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

- gewichtstoename/zwaarlijvigheid
- vollemaansgezicht, grote buikomvang (centrale obesitas), (syndroom van Cushing)
- dunner worden van de huid, dit kan leiden tot streepvormige littekens (striae)
- rimpeling van de huid
- droge huid
- het zichtbaar worden van bloedvaten onder het huidoppervlak (teleangiëctastieën)
- pigmentatieveranderingen
- overmatige haargroei (hypertrichose)
- haarverlies/gebrek aan haargroei (alopecia)/ haar dat er beschadigd uitziet (trichorrhexis)
- vertraagde gewichtstoename
- langzame groei

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

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

Heeft uw kind veel last van een bijwerking? Of heeft uw kind een bijwerking die hier 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 hoef 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/geen*** toestemming om mijn kind deel te laten nemen aan het interventiedeel van het onderzoek als hij/zij een opvlamming heeft van het eczeem, zoals te lezen is in de informatiebrief.
- Ik geef **wel/geen*** 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: __ / __ / __

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* 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.

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_____

Introduction			
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, 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 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 variable (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_____

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	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			
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
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
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 reference 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
	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
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Figure 2
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

*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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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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Authors' contributions

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

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Competing interests

There are no competing interests for any authors.

Trial registration

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

Abstract

Introduction

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

Methods and Analysis

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

Ethics and Dissemination

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

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. The study protocol is approved by the Medical Ethics Committee (MEC) of the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2017-328). The results of the study will be published in international peer-reviewed journals and presented at national and international conferences.

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. (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

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

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

Objectives

To determine whether initial treatment with a potent TCS is more effective than a mild TCS in the treatment of children with a moderate flare-up of AD in primary care in the short (i.e. 1 week and 4 weeks of follow-up) and long-term (i.e. 6 months follow-up) control of the disease.

In the observational cohort, the aim is to determine the frequency and determinants of flare-ups of AD. Furthermore, we will explore the burden of AD by measuring severity, medication use, healthcare use and quality of life (QoL) during 1-year follow-up.

Study design

The Rotterdam Eczema study is an observational cohort study with an embedded

pragmatic randomized open-label superiority trial with two groups and a patient-reported primary outcome of long-term control. See flowchart in figure 1.

Methods; participants, interventions and outcomes

Healthcare system

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

Study setting

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

Eligibility criteria

To be eligible to participate in the cohort study, a child must meet all of the following criteria: aged between 12 weeks and 18 years, diagnosis of eczema (ICPC code S87 and S88 or prescription of topical treatment for eczema) plus confirmation of the diagnosis by the GP, a consultation or repeated prescription in the previous 12 months, and informed consent. Exclusion criteria for the cohort study are: as determined by the own GP. The own GP will check the list of selected children, the own GP is aware of potential problems limiting participation in a trial like family problems eg circumstances such as ongoing problems due to divorcing parents, relevant psychosocial problems, a seriously ill family member or if the child has serious comorbidities (eg intellectual disability)..Furthermore, exclusion criteria are: currently under treatment with a dermatologist, contra-indications for the study medication, language barrier, or no access to internet (necessary to fill in weekly online questionnaire).

The inclusion criteria for the trial part of the study are: participation in the cohort, flare-up (i.e. need to intensify topical treatment) from the child's and/or parents' point of view,

a Three Item Severity (TIS) score from ≥3 to <6. Exclusion criteria for the trial part are: use of TCS in the 2 weeks before inclusion in the trial, AD on eyelid(s), >50% of body affected by AD, other skin disorders hampering proper assessment of eczema, pregnancy and or breastfeeding, or untreated skin infections (bacterial, viral, fungal or parasitic).

Interventions

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

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

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

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

always be advised to use indifferent therapy with a standard emollient (i.e. 'cetomacrogol'). The advice is to use the emollients daily.

Patient and Public Involvement

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

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

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

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

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. See table 1 for an overview of observations made during the 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; clear, almost clear, mild, moderate, severe, very severe), ix) itch intensity score (the numeric rating scale-11 is ranging from 0, no itch to 10, worst itch imaginable), and x) healthcare use (i.e. telephone contact with GP, consultation at the general practice, or referral to secondary care).

The QoL questionnaires are the IDQOL and CDLQI: both are validated and widely used in dermatology as a QoL scale for children aged ≤4 years and aged 4-16 years, respectively. (22, 23). The use of medication will be registered by weighing the tube of TCS after 1 week, 4 weeks and 24 weeks in the trial. Furthermore, in the weekly questionnaire, the children will register the amount of days that TCS and neutral ointment were used in the previous week.

The aim of the observational cohort is to determine the frequency and determinants of flare-ups of AD after 1-year follow-up.

Secondary outcomes concerning the cohort includes disease severity at inclusion, and at 26 weeks and 52 weeks follow-up using POEM and EASI, QoL, frequency of flare-ups, medication use, and healthcare use

Table 1. Schedule of observations made during the study

Outcomes collected	*Cohort*				*Trial*				
	Baseline	**Week 26**	**Week 52**	**Weekly for 52 weeks**	**Baseline**	**Week 1**	**Week 12**	**Week 24**	**Weekly for 24 weeks**
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	V	V	
Weigth						V		V	
Length						V		V	
Head circumference						V		V	
Weigh medication						V	V	V	

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

Sample size

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

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). (2) 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 patie1nt'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 weekly questionnaires include a question on who completed the questionnaire, the child, the parent or together. We can therefore take into account by whom the questionnaire has been completed in our analysis. If patients are 16 years or older, they will complete the questionnaires themselves. Children under 16 are free in their choice to complete the questionnaire themselves or together with / by a parent.The physician assistants will received 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.

Safety reporting

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

Monitoring

Due to the characteristics of this study it is not necessary to install a Data Safety Monitoring Board. Nevertheless, the study will be monitored as described in the ICH-GCP Guidelines (chapter 5.18). The department of General Practice has developed a monitoring plan and monitoring checklist (based on the ICH-GCP Guidelines) which will

be used in this study. A senior researcher (project leader) will be designated as monitor. This senior researcher is not related to the current project and is part of another research discipline within the department. At various moments in the study (not known to the researcher in front) an appointment will be made with the researcher and projectleader of the current project to monitor the study by making use of the checklist of the department of general practice.

Adverse events

All (serious) adverse events and suspected unexpected serious adverse reactions reported spontaneously by the subject or observed by the investigator or the staff will be recorded.

Discussion

This will be the first study to investigate the effectiveness of treatment with TCS class I vs class III on long-term control over 6-months follow-up of children in primary care with AD.

We chose an observational cohort design with an embedded pragmatic randomized 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. (9, 10) Therefore, it was particularly important to design a trial with a validated participant-reported primary outcome.

The structure of regular home visits will probably artificially improve treatment adherence. It is generally known that treatment adherence is highest immediately after seeing a doctor. (26) Both treatment arms will receive home visits, so this effect will be equally spread. The home visits will influence the generalizability of the results. However, it is crucial for several outcome measures to visit the patients. We kept the 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 children with AD are treated by a GP (only about 1% is referred to secondary care) and

have a milder form of AD as compared to patients treated by a dermatologist. (2) Whether the effects of initial treatment with a potent TCS as experienced in a specialist setting can be transferred to treatment in primary care is unknown. Since the present study will focus on these gaps, it will hopefully make an important contribution to knowledge with respect to the use of local corticosteroids in children with AD treated in general practice.

Figure legend

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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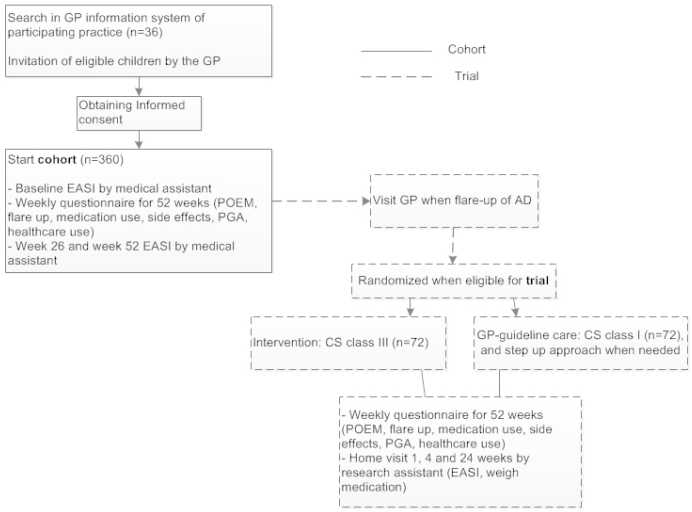

Figure 1. Flow chart of the study.

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_____

Introduction			
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, 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 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 variable (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_____

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	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			
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
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
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 reference 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
	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
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__10_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a_____
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_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____1_____
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_____
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_____
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_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___n/a_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___Figure 2_____
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_____

*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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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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Authors' contributions

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

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Competing interests

There are no competing interests for any authors.

Trial registration

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

Abstract

Introduction

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

Methods and Analysis

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

Ethics and Dissemination

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

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. The study protocol is approved by the Medical Ethics Committee (MEC) of the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2017-328). The results of the study will be published in international peer-reviewed journals and presented at national and international conferences.

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. (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

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

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

Objectives

To determine whether initial treatment with a potent TCS is more effective than a mild TCS in the treatment of children with a moderate flare-up of AD in primary care in the short (i.e. 1 week and 4 weeks of follow-up) and long-term (i.e. 6 months follow-up) control of the disease.

In the observational cohort, the aim is to determine the frequency and determinants of flare-ups of AD. Furthermore, we will explore the burden of AD by measuring severity, medication use, healthcare use and quality of life (QoL) during 1-year follow-up.

Study design

The Rotterdam Eczema study is an observational cohort study with an embedded

pragmatic randomized open-label superiority trial with two groups and a patient-reported primary outcome of long-term control. See flowchart in figure 1.

Methods; participants, interventions and outcomes

Healthcare system

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

Study setting

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

Eligibility criteria

To be eligible to participate in the cohort study, a child must meet all of the following criteria: aged between 12 weeks and 18 years, diagnosis of eczema (ICPC code S87 and S88 or prescription of topical treatment for eczema) plus confirmation of the diagnosis by the GP, a consultation or repeated prescription in the previous 12 months, and informed consent. This will be checked by the own GP and the researcher. Exclusion criteria for the cohort study are: as determined by the own GP. The own GP will check the list of selected children, the own GP is aware of potential problems limiting participation in a trial like family problems eg circumstances such as ongoing problems due to divorcing parents, relevant psychosocial problems, a seriously ill family member or if the child has serious comorbidities (eg intellectual disability). Furthermore, exclusion criteria are: currently under treatment with a dermatologist, contra-indications for the study medication, language barrier, or no access to internet (necessary to fill in weekly online questionnaire).

The inclusion criteria for the trial part of the study are: participation in the cohort, flare-up (i.e. need to intensify topical treatment) from the child's and/or parents' point of view, a Three Item Severity (TIS) score from ≥3 to <6. Exclusion criteria for the trial part are: use of TCS in the 2 weeks before inclusion in the trial, AD on eyelid(s), >50% of body affected by AD, other skin disorders hampering proper assessment of eczema, pregnancy and or breastfeeding, or untreated skin infections based on clinical signs and symptoms (bacterial, viral, fungal or parasitic).

Interventions

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

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

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

from the child's own pharmacy.

Besides the use of corticosteroids, all children (control and intervention group) will always be advised to use indifferent therapy with a standard emollient (i.e. 'cetomacrogol'). The advice is to use the emollients daily.

Patient and Public Involvement

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

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

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

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

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. See table 1 for an overview of observations made during the 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; clear, almost clear, mild, moderate, severe, very severe), ix) itch intensity score (the numeric rating scale-11 is ranging from 0, no itch to 10, worst itch imaginable), and x)

healthcare use (i.e. telephone contact with GP, consultation at the general practice, or referral to secondary care).

The QoL questionnaires are the IDQOL and CDLQI: both are validated and widely used in dermatology as a QoL scale for children aged ≤4 years and aged 4-16 years, respectively. (22, 23). The use of medication will be registered by weighing the tube of TCS after 1 week, 4 weeks and 24 weeks in the trial. Furthermore, in the weekly questionnaire, the children will register the amount of days that TCS and neutral ointment were used in the previous week.

The aim of the observational cohort is to determine the frequency and determinants of flare-ups of AD after 1-year follow-up.

Secondary outcomes concerning the cohort includes disease severity at inclusion, and at 26 weeks and 52 weeks follow-up using POEM and EASI, QoL, frequency of flare-ups, medication use, and healthcare use.

Table 1. Schedule of observations made during the study.

Outcomes collected	*Cohort*				*Trial*				
	Baseline	Week 26	Week 52	Weekly for 52 weeks	Baseline	Week 1	Week 4	Week 24	Weekly for 24 weeks
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	V	V	
Weigth						V		V	
Length						V		V	
Head circumference						V		V	
Weigh medication						V	V	V	

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

Sample size

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

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). (2) 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 patie1nt'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 weekly questionnaires include a question on who completed the questionnaire, the child, the parent or together. We can therefore take into account by whom the questionnaire has been completed in our analysis. If patients are 16 years or older, they will complete the questionnaires themselves. Children under 16 are free in their choice to complete the questionnaire themselves or together with / by a parent.The physician assistants will received 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.

Safety reporting

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

Monitoring

Due to the characteristics of this study it is not necessary to install a Data Safety Monitoring Board. Nevertheless, the study will be monitored as described in the ICH-GCP Guidelines (chapter 5.18). The department of General Practice has developed a

monitoring plan and monitoring checklist (based on the ICH-GCP Guidelines) which will be used in this study. A senior researcher (project leader) will be designated as monitor. This senior researcher is not related to the current project and is part of another research discipline within the department. At various moments in the study (not known to the researcher in front) an appointment will be made with the researcher and projectleader of the current project to monitor the study by making use of the checklist of the department of general practice.

Adverse events

All (serious) adverse events and suspected unexpected serious adverse reactions reported spontaneously by the subject or observed by the investigator or the staff will be recorded.

Discussion

This will be the first study to investigate the effectiveness of treatment with TCS class I vs class III on long-term control over 6-months follow-up of children in primary care with AD.

We chose an observational cohort design with an embedded pragmatic randomized 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. (9, 10) Therefore, it was particularly important to design a trial with a validated participant-reported primary outcome.

The structure of regular home visits will probably artificially improve treatment adherence. It is generally known that treatment adherence is highest immediately after seeing a doctor. (26)Both treatment arms will receive home visits, so this effect will be equally spread. The home visits will influence the generalizability of the results. However, it is crucial for several outcome measures to visit the patients. We kept the

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

children with AD are treated by a GP (only about 1% is referred to secondary care) and have a milder form of AD as compared to patients treated by a dermatologist. (2) Whether the effects of initial treatment with a potent TCS as experienced in a specialist setting can be transferred to treatment in primary care is unknown. Since the present study will focus on these gaps, it will hopefully make an important contribution to knowledge with respect to the use of local corticosteroids in children with AD treated in general practice.

Figure legend

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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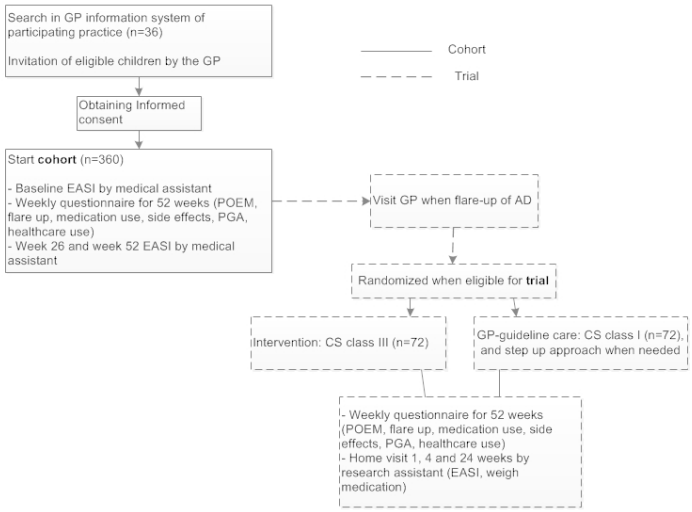

Figure 1. Flow chart of the study.

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_____

Introduction			
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, 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 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 variable (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_____

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	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			
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
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
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 reference 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
	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
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__10_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a_____
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_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____1_____
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_____
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_____
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_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___n/a_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___Figure 2_____
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_____

*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.