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Different strategies for using topical corticosteroids in people with eczema (Protocol)

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[Intervention Protocol]

Different strategies for using topical corticosteroids in people with eczema

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To establish the effectiveness and safety of different ways of using topical corticosteroids in people with eczema.

BACKGROUND

Description of the condition

Eczema (also called 'atopic dermatitis' or 'atopic eczema') is a chronic inflammatory skin condition, characterised by dry itchy skin with eczematous lesions, which typically fluctuates between periods of remission and flares. Eczema often occurs concurrently with atopic diseases including asthma, allergic rhinitis/hay fever and food allergy. These diseases share a common pathogenesis,

and frequently present together in the same individual and family. 'Atopy' refers to the genetic tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of common environmental proteins such as pollen, house dust mite, and food allergens (Stone 2002; Thomsen 2015). Around 30% of people with eczema develop asthma and 35% develop allergic rhinitis (Luoma 1983). However, it is known that atopy does not concurrently occur in all patients with atopic eczema. In view of this, there have been recent proposals to use the term 'eczema' to define patients both with and without atopy. In agreement with

the 'Revised nomenclature for allergy for global use' (Johansson 2004), and for consistency with other Cochrane Reviews evaluating eczema therapies (van Zuuren 2017), we will use the term 'eczema' throughout the review.

Eczema is a common condition throughout the world affecting approximately one in five children, and up to 5% of adults (Barbarot 2018; Odhiambo 2009). The incidence of eczema is highest in the first year of life and can often resolve during childhood (Ban 2018; Kim 2016). However, a recent review has shown that persistence into adolescence and early adulthood may be more common than previously thought, particularly for those with persistent and severe disease or late onset disease (Abuabara 2018).

Eczema can have a significant impact on quality of life (Eckert 2017); and there is a high burden associated with eczema when compared to other skin diseases (Hay 2014). Both the individual and their family can be affected by the disease through factors including disturbed sleep due to itching and scratching, time off work or school for frequent visits to healthcare professionals, restrictions to daily activities, and the need to apply daily time-consuming treatments (Drucker 2016; Eckert 2018).

Clinical features

Eczema may be acute (short and severe) with weeping vesicles on red, swollen skin, or it may be chronic (long-term) with inflammation, lichenification (thickening of the skin caused by repeated rubbing or scratching), excoriation (abrasion because of rubbing or scratching), hyperpigmentation, and exaggerated surface markings (Weidinger 2016). The typical distribution and type of lesions vary during different stages of life and between different ethnicities. In infants, the extremities and face are usually affected. By around two years of age, lesions mainly appear on the limbs, particularly in the creases of the elbows and knees, as well as the neck, wrists, and ankles. In adulthood, the lesions can become more widespread than those seen in childhood (Bieber 2008a). The severity of eczema can vary enormously, ranging from dry skin with the occasional itchy inflamed patch, to involvement of the whole body with secondary infections. The course of eczema may also vary from a relapsing-remitting one affecting a few areas recurrently to a continuous one with prolonged periods of inflamed skin covering most of the body (Berke 2012). Itching can induce a vicious cycle of scratching, leading to skin damage, which in turn causes itchiness-often referred to as the 'itch-scratch cycle' (Pavlis 2017).

Treatment of eczema

There is currently no cure for eczema, so the treatment goal is control of the disease using the wide range of treatments available including emollients (NICE 2007; SIGN 2011). First-line therapy is the daily application of emollients combined with anti-inflammatory therapy. The most commonly used anti-inflamma-

tory therapy is topical corticosteroids, but topical calcineurin inhibitors are also used. These can be combined with bandages and phototherapy for those who do not respond sufficiently to topical treatment alone. Severe eczema may require systemic treatments such as oral ciclosporin, methotrexate or azathioprine. New biologic agents such as dupilumab are now available for cases of eczema that do not respond to other systemic treatments (Snast 2018). Although topical corticosteroids have been the mainstay of eczema treatment for over 60 years, there are still many unanswered questions about how best to use them (Batchelor 2013).

Description of the intervention

Topical corticosteroids were first introduced in the 1950s when topical hydrocortisone was found to improve various dermatoses (Sulzberger 1952). Since then, a huge number of topical corticosteroids of increased potency have been developed, and are available in various formulations such as creams and ointments. Mometasone furoate is one of the newer generation of products developed with the intention of producing a safer potent topical corticosteroid (Prakash 1998). Topical corticosteroids are all classified by their potency from mild through to very potent, although the classification of potency varies around the world (British National Formulary 2018; World Health Organization (WHO) 1997). The choice of potency to be used is based on age, body site to be treated and severity of eczema. Low- to moderate-potency topical corticosteroids are usually sufficient for mild eczema and are also used on sensitive skin such as the face and flexural areas. Potent or very potent topical corticosteroids are usually used in severe, thick eczematous plaques over thicker skin sites, such as limbs and palmoplantar surfaces. The advice is to use topical corticosteroids, of appropriate potency, once a day until the eczema is controlled, then 'as required' (NICE 2007).

Local side effects of topical corticosteroids include the possibility of skin atrophy (skin thinning), striae (stretch marks) and purpura (discolouration), whilst systemic side effects include hypothalamic pituitary axis (HPA) suppression and growth suppression (Callen 2007). Skin thinning and effects on growth and development have been reported to be the main concerns amongst people using topical corticosteroids (Li 2017). Side effects of topical corticosteroids are thought to be rare in usual practice and are more likely to occur if topical corticosteroids have been used inappropriately, such as continuous use or if potent corticosteroids are applied to areas which have high permeability (e.g. eyelids) (Callen 2007; Nankervis 2016). This inappropriate use could lead to systemic side effects such as hypothalamic pituitary axis suppression or hyperglycaemia (Gilbertson 1998). But despite their relative safety, concerns and confusion about the use of topical corticosteroids amongst people with eczema and the healthcare professionals who treat them are widespread. Negative beliefs about the use of topical corticosteroids are thought to contribute to poor treatment adherence (Aubert-Wastiaux 2011; Li 2017; Teasdale 2017).

Topical corticosteroids have traditionally been used reactively (in response to a worsening of the eczema) to control inflammation under the skin. They work by reducing skin inflammation by acting on a number of inflammatory pathways. They bind to glucocorticoid intracellular receptors which then results in a number of anti-inflammatory actions. These include: inhibition of phospholipase A2 activity resulting in reduced production of lipid mediators; inhibition of cyclooxygenase induction causing decreased prostaglandin production; inhibition of nitric oxide synthase production; inhibition of cytokine causing suppression of cell-mediated inflammation; inhibition of mast cell activity resulting in decreased levels of mast cell inflammatory mediators; and vasoconstriction (local blood flow reduction) (Ahluwalia 1998).

A number of different ways (or 'strategies') of using topical corticosteroids for treating eczema have been proposed. Proactive use of topical corticosteroids for two days per week between flares is thought to help to prevent eczema flares and therefore reduce the need for more intense periods of topical corticosteroid use to treat flares which may be associated with an increase in adverse events (Schmitt 2011). Applying topical corticosteroids to wet skin after bathing or use of wet wraps may increase penetration through the skin and increase delivery of the cream or ointment into the upper layers, thus increasing efficacy of the topical corticosteroid (Gonzalez-Lopez 2017; Kohn 2016). Topical calcineurin inhibitors (pimecrolimus or tacrolimus) can be used instead of topical corticosteroids and a strategy of alternating between these two treatments may be as effective as using topical corticosteroids alone, but may reduce the adverse events associated with topical corticosteroids, such as skin thinning (Broeders 2016).

Some strategies aim to reduce adverse events whilst increasing or maintaining effectiveness of the topical corticosteroid. Applying topical corticosteroids once daily may be as effective as two or more times a day but may reduce the likelihood of adverse events occurring (Green 2004). Another strategy is to use different potency topical corticosteroids, possibly combined with different duration of use, such as a more potent topical corticosteroid for a shorter period compared to milder potency topical corticosteroids for a longer duration. This reduces the length of time the topical corticosteroid would be used although more potent topical corticosteroids may be associated with increased adverse events (Thomas 2002).

Since topical corticosteroids are used with emollients, other proposed strategies concern the combined use of these two treatments, such as the order in which the treatments are applied and the optimum time lapse between application of each treatment. Current guidance in the UK from the National Health Service (NHS) is to apply emollients first then wait for 30 minutes before applying the topical corticosteroid for maximal benefit (NHS 2019). Additionally, different preparations of topical corticosteroids (e.g. ointments, creams) have been developed to increase the efficacy; and different concentrations (e.g. hydrocortisone 0.5% versus 2.5%). More recently, 'second generation' once-

daily topical corticosteroids (mometasone furoate and fluticasone propionate) have been proposed as a safer and effective alternative to the older topical corticosteroid preparations (Bieber 2008b).

Why it is important to do this review

It is well established that some patients, parents and clinicians have considerable concerns about using topical corticosteroids for treating eczema (Charman 2000; Li 2017; Teasdale 2017). As a result, topical corticosteroids are often under-used in Western countries, resulting in poorly controlled disease (Lundin 2018). Conversely, in other areas of the world, such as India, potent topical corticosteroid use is often unregulated and patients are able to obtain these steroids over the counter. Subsequent inappropriate use of potent topical corticosteroids can lead to an increase in adverse events (Coondoo 2014).

This situation is exacerbated by the lack of clarity as to how the different ways of using topical corticosteroids - such as once-a-day or twice-a-day application, increasing topical corticosteroid potency in response to a flare, or twice-a-week use to proactively prevent flares - affect both effectiveness and safety profile. The British National Formulary (BNF) provides little reassurance, describing adrenal suppression as rare but providing no quantification of other side effects (British National Formulary 2018). Concerns and uncertainties around topical corticosteroids were highlighted in the James Lind Alliance Priority Setting Partnership for eczema, in which the following two topics relating to topical corticosteroid safety were identified by patients and healthcare professionals as priority areas for research (Batchelor 2013).

- "What is the best and safest way of using topical corticosteroids?"
- "What is the long-term safety of topical corticosteroids?"

This comprehensive systematic review is needed to summarise the available evidence on the effectiveness and safety of different ways of using topical corticosteroids to support patients and clinicians in making informed treatment choices. However, since most eczema trials have a relatively short follow-up, this review will primarily address the first of these two questions.

The strategies included in this review will refer to different methods of using topical corticosteroids to improve effectiveness or safety, or both, and hence achieve the best outcomes for the patients. A strategy may aim to improve the long-term control of eczema, for example, in the case of proactive topical corticosteroid treatment. This strategy involves weekly application of topical corticosteroid, for two consecutive days, to previously affected or new sites of eczema, to reduce the risk of flares (Schmitt 2011). Alternatively, a strategy such as reducing the frequency of application may be designed to improve the safety of the drug whilst maintaining effectiveness (Green 2004; Williams 2007).

This review forms part of a body of work funded by the National Institute for Health Research (NIHR) Programme Grants

for Applied Research (grant no: RP-PG-0216-20007) to develop an online behavioural intervention to support self-care of eczema in children, adolescents and young adults (Eczema Care Online, ECO), and the findings will contribute to development of the intervention by providing data on the best and safest ways to use topical corticosteroids.

This review will be complemented by another ongoing Cochrane Review which will incorporate a network meta-analysis: "Topical treatments for eczema: a network meta-analysis". The ongoing Cochrane Review will compare topical corticosteroids to other topical treatments, such as topical calcineurin inhibitors.

OBJECTIVES

To establish the effectiveness and safety of different ways of using topical corticosteroids in people with eczema.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) where randomisation is at any level (including cluster and within-participants trials).

Types of participants

Participants of any age and gender with a diagnosis of eczema (also known as atopic dermatitis or atopic eczema) of any severity by a healthcare professional, or using established diagnostic criteria for eczema (e.g. the standardised diagnostic criteria of Hanifin and Rajka (Hanifin 1980) or the UK Working Party diagnostic criteria for atopic dermatitis (Williams 1994)). We will also accept modified versions of standard diagnostic criteria.

Studies which include participants with other types of eczema such as contact dermatitis, varicose eczema, and seborrhoeic eczema, or other inflammatory or 'steroid-responsive' skin conditions such as psoriasis, will only be included if the trial also includes people with eczema and the data are reported separately.

Types of interventions

The intervention will be any topical corticosteroid of any preparation and potency in a trial where one strategy of using the topical corticosteroid is compared to a different strategy. This will include, but not necessarily be limited to, the following strategies.

Different strategies for topical corticosteroid use

- Proactive versus reactive topical corticosteroid treatment (e.g. twice per week versus 'as required').
- Frequency of application of topical corticosteroid (e.g. once daily versus twice daily).
- Duration of use of topical corticosteroids for induction of remission (e.g. short term versus long term).
- Different time of day for applying topical corticosteroids, and order of application or timing between applications of topical corticosteroids and emollients (e.g. evening versus morning, immediately following a bath/shower versus no guidance).

Different preparations or potencies of topical corticosteroids

- Different potencies of topical corticosteroids (e.g. mild versus moderate; stepping up or stepping down potency of topical corticosteroids).
- Different preparations but the same topical corticosteroid (e.g. ointment versus cream), including proprietary topical corticosteroid versus the generic equivalent (e.g. Elocon versus mometasone furoate 0.1%).
- Different concentrations of topical corticosteroids (e.g. hydrocortisone 0.5% versus hydrocortisone 2.5%).

Topical corticosteroids alongside other interventions

- Alternating between topical corticosteroids and calcineurin inhibitors (e.g. topical corticosteroids alone versus alternating between topical corticosteroids and topical calcineurin inhibitors).
- Use of topical corticosteroids under occlusion (e.g. with wet wraps versus no wet wraps).

Other strategies

- Second generation topical corticosteroids (mometasone furoate and fluticasone propionate) against first generation topical corticosteroids of the same potency (e.g. mometasone furoate 0.1% versus betamethasone valerate 0.1%).
- A combination of any of the strategies above (e.g. short burst of potent topical corticosteroid versus longer duration of mild topical corticosteroids).
- Any other strategies for using topical corticosteroids not listed above.

Since the focus of this review is to compare different strategies of using topical corticosteroids, the following comparisons will be excluded.

- Topical corticosteroid compared with either no treatment, vehicle or placebo (unless it is specifically assessing an alternative regimen such as proactive therapy).

- Topical corticosteroid compared with another topical corticosteroid of the same potency and preparation but no differences in how they are used.
- Topical corticosteroid compared with different topical treatments such as calcineurin inhibitors or emollients.
- Topical corticosteroid compared with systemic treatments.
- Topical corticosteroid treatment in conjunction with an eczema treatment used for the most severe cases of eczema as defined by NICE (i.e. phototherapy and systemic therapy) (NICE 2018). This is because it will be difficult to detect any differences in efficacy or safety between the topical corticosteroids strategies when such treatments are also used.

Types of outcome measures

We will assess both effectiveness and safety to reflect the overall aim of this review.

The effectiveness outcomes of interest for this review are focused on the two domains for which the international Harmonizing Outcome Measures for Eczema (HOME) initiative has recommended core outcome measurement instruments i.e. clinician-reported signs and patient-reported symptoms of eczema (HOME). There is currently no agreed standardised timing for effectiveness outcome assessments for eczema trials. Therefore, to assess treatment effects in a consistent way, we will focus on short-term effectiveness outcomes reported between one and four weeks (taking the earliest available time point within that range), medium-term effectiveness outcomes between 12 and 16 weeks (taking the closest time point to 12 weeks), and long-term effectiveness as the longest time point greater than 16 weeks.

We will also report outcomes at baseline, end of treatment, and end of follow-up regardless of timing. We will attempt to pool data at similar time points where possible.

Because many different instruments are used to assess effectiveness of treatments for eczema (Schmitt 2007), we will use a hierarchical approach in which we will initially extract data from one instrument per outcome based on the priority order described below. However, we will also make a note of other instruments reported, and data from other lower priority instruments may also be extracted to maximize our ability to summarise data in pooled analyses. Where possible, we will also compare the effect sizes calculated in this review against the minimal clinically important differences (MCID) from the literature.

Throughout this review, we will use the term 'effectiveness' to describe both 'efficacy' and 'effectiveness'. In many trials it is likely to be unclear whether the trial is primarily assessing efficacy or effectiveness and we would prefer to avoid making inappropriate judgements.

Safety outcomes of interest reflect the side effects of topical corticosteroids. We define 'relevant' adverse events as those previously identified as being of particular concern to patients (Li 2017), the side effects listed in the Summary of Product Characteristics for

topical corticosteroids used to treat eczema, and original data submissions from the Eczema Priority Setting Partnership, outlining patients' and clinicians' concerns about the safety of topical corticosteroids (Batchelor 2013). We will report data on individual relevant adverse events and their relatedness to the study drug where available. Where appropriate, the total number of relevant adverse events per treatment group will be reported to allow pooling of data. We will present safety data for the treatment and follow-up periods separately where possible. Where outcomes are assessed during post-treatment follow-up, we will only include data where participants are retained in their randomised groups. We will not use long-term safety data from crossover or within-participant trials due to the high likelihood of contamination.

For safety data, we will report adverse events at the end of treatment and the end of follow-up (where specified).

Primary outcomes

Two primary outcomes are included - safety and effectiveness (clinician-reported signs of eczema) - to reflect the overall aim of this review.

- **Changes in clinician-reported signs of eczema (effectiveness).** We will extract data based on the following priority order of instruments.
 - Eczema Area and Severity Index (EASI) - this is the HOME recommended core outcome measurement instrument for clinician-reported signs of eczema (Hanifin 2001;Schmitt 2014).
 - Objective SCORing Atopic Dermatitis (ObjSCORAD) - measures similar aspects of the disease to EASI (Kunz 1997;Oranje 2007).
 - SCORing Atopic Dermatitis (SCORAD) - most commonly used instrument in eczema trials, comprising objective SCORAD plus itch and sleep loss (Kunz 1997;Oranje 2007)
 - Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score (Berth-Jones 1996).
 - Three Item Severity score (TIS) (Oranje 2007;Willemsen 2009;Wolkerstorfer 1999).
 - Investigator Global Assessment (IGA) - no validated instrument and little consistency between trials but commonly included (Futamura 2016).
 - Any other instruments.

- **Number of relevant local adverse events (safety).** This will include skin thinning, striae, telangiectasia, aging/wrinkling, changes in skin colour, sensitisation, skin bleaching, worsening or induction of acne, skin infections, folliculitis, perioral/periorcular dermatitis, and application site reactions such as burning sensation/stinging. In our analyses, we will primarily focus on the number of participants with at least one adverse event.

Secondary outcomes

● Patient-reported symptoms of eczema (effectiveness).

Data will be extracted based on the following priority order of instruments.

- Patient-Oriented Eczema Measure (POEM) - recommended core instrument by HOME for the patient-reported symptoms of eczema (Charman 2004; Spuls 2017).
- Patient-Oriented SCORAD (PO-SCORAD) (Vourc'h-Jourdain 2009).
- Sleep and itch scales, as measured by Visual Analogue Scales (VAS) or Numerical Rating Scales (NRS).
- Self-Administered EASI (SA-EASI) (Housman 2002).
- Patient Global Assessment (PGA) - no validated instrument and little consistency between trials.
- Any other instruments.

● Number of relevant systemic adverse events (safety).

This will include bone problems, impact on growth and development, effects on endocrine system, eye problems, and cancer. In our analyses, we will primarily focus on the number of participants with at least one adverse event.

Search methods for identification of studies

We aim to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist will search the following databases for relevant trials with no restriction by date.

- the Cochrane Skin Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE via Ovid (from 1946 onwards);
- Embase via Ovid (from 1974 onwards);
- the GREAT database (Global Resource for Eczema Trials (Centre of Evidence Based Dermatology); www.greatdatabase.org.uk).

The Information Specialist has devised a draft search strategy for RCTs for MEDLINE (Ovid), which is displayed in Appendix 1. We will use this as the basis for search strategies for the other databases listed.

Trial registers

We (EA, JH) will search the following trial registers using the search terms 'eczema' and 'atopic dermatitis'.

- the ISRCTN register (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);

- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

Searching reference lists

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

Correspondence with trialists

We will contact trialists for clarification and further data if trial reports are unclear.

Adverse effects

We will not perform a separate search for adverse effects of the target interventions. We will consider adverse effects described in included studies only.

Data collection and analysis

We will use Covidence systematic review software to screen and manage the references, and to record the data extracted from the included studies. The software will also automatically create a study flow diagram (PRISMA) for us to include in the review (Liberati 2009).

Selection of studies

Two review authors (EA, JH) will independently screen the titles and abstracts of each record identified in the searches. If a study meets our inclusion criteria, we will analyse the full text to confirm its inclusion. Any disagreement will be resolved by a third reviewer (JRC, KST or HCW). We will record reasons for exclusions in the 'Characteristics of excluded studies' table. We will present the process of trial selection in a PRISMA flow diagram (Liberati 2009).

Data extraction and management

Two review authors (EA, JH) will independently extract data from each included study using a data extraction form. We will pilot and modify the form, as necessary. The following data will be extracted.

- Study population (e.g. inclusion criteria, setting/country, severity of eczema, age, gender, ethnicity)
- Study methods (e.g. study design, blinding methods, funding source)
 - Interventions and comparators (e.g. treatment name, potency, frequency of use)
 - Primary and secondary outcomes (including time points - both during treatment and during follow-up)

We will enter study characteristics into a 'Characteristics of included studies' table; and we will analyse or narratively describe extracted outcome data. We will resolve any disagreements during the data extraction phase through discussion with a third author (JRC, KST, or HCW).

We will include multiple reports of a trial but will choose a primary reference and list the others as secondary references.

We will also extract study characteristics for ongoing trials to produce a 'Characteristics of ongoing studies' table. We will do the same for 'Studies awaiting classification' where there is not enough information available for us to include or exclude the trial in the review.

Assessment of risk of bias in included studies

Two authors (EA, JH) will independently assess the risk of bias of each included study using the Cochrane 'Risk of bias' tool (Higgins 2011). The following domains will be assessed.

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding of participants and study personnel)
 - Detection bias (blinding of outcome assessment)
 - Attrition bias (completeness of data, missing data and losses to follow-up, intention to treat principle)
 - Reporting bias (selective reporting of outcomes, assessed via comparing with the study's protocol or clinical trial register entry)
 - Other bias (including design-specific risks of bias, baseline imbalance, contamination, fraud, selective reporting of subgroups)

Each domain will be assessed as low, unclear or high risk of bias. Disagreements will be resolved via discussion with a third author (JRC, KST or HCW). We will present a 'Risk of bias' graph and 'Risk of bias' summary figure in the review.

Measures of treatment effect

We will report dichotomous data as risk ratios (RR) with associated 95% confidence intervals (CI). Continuous data will be reported as mean differences (MD) with associated 95% CIs where the same scale is used to measure an outcome. Where appropriate, we may consider using a standardised mean difference (SMD) and associated 95% CI when different instruments are used to measure

effectiveness outcomes (i.e. clinician-reported signs and patient-reported symptoms).

For adverse event data, we will focus on analysing the number of participants with at least one adverse event, and hence we will report RR. However, in some studies the number of events per arm may only be reported and it will not be clear if multiple adverse events occurred within the same individual. For these studies, we will contact the authors to request data in the format of 'number of participants with at least one adverse event'. If we are unable to obtain these data, we will analyse these data as count data, following guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and produce rate ratios instead of RR. Where studies report time-to-flare data based on a measure of effectiveness (e.g. EASI), we shall extract hazard ratios (HR) from the study reports.

Unit of analysis issues

The unit of analysis will primarily be the individual participant. If only count data is available for adverse events, we will analyse the number of events over time and calculate rate ratios. We will only meta-analyse cluster RCTs with parallel RCTs if the data reported in the trial publication has been correctly analysed, taking into account the number of clusters. If appropriate, we may try to estimate the intracluster correlation coefficient to enable us to include the trial in the meta-analysis (Higgins 2011).

For within-participant trials, we will extract paired data from the study report and analyse separately to parallel RCTs. If paired data are not available, we will attempt to estimate the paired data using appropriate methods and guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Hirji 2011). If this is not possible, we will only use data from the first part of the study in cross-over trials, or narratively describe the results.

For within-participant trials where body parts receive different interventions, we will not extract data on outcomes which affect the whole body (e.g. systemic adverse events), as it will not be possible to determine which treatment caused the event.

For studies which include multiple intervention groups, we will either analyse each intervention group versus a comparator in a separate analysis, or combine groups to create a single pair-wise comparison, if clinically appropriate (Higgins 2011).

Dealing with missing data

Where possible we will conduct an intention-to-treat analysis, including all randomised participants where data is provided. If data is missing, we will contact study authors and produce a table in the review detailing such contact (e.g. dates, information requested, whether they replied). We will conduct sensitivity analyses, removing studies at high risk of attrition bias and will also consider attrition bias when undertaking our quality assessments (Schünemann 2013). For continuous data, we will attempt to calculate any missing statistics (e.g. standard deviations) using the methods described

in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

When pooling studies in a meta-analysis, we will consider any methodological and clinical differences between studies, and only include studies in the same meta-analysis where it is considered appropriate. We will assess heterogeneity through forest plot inspection and the I^2 statistic using the thresholds defined in the *Cochrane Handbook for Systematic Reviews of Interventions*: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% represents considerable heterogeneity (Higgins 2011). If we identify substantial or considerable statistical heterogeneity, we will attempt to determine reasons by examining the study characteristics and performing subgroup analyses where appropriate.

Assessment of reporting biases

If we include 10 or more studies in a meta-analysis, we will produce a funnel plot to explore publication bias (Sterne 2011). We will describe narratively suspected reporting biases and their potential effects on the overall results and conclusions.

Data synthesis

We will narratively synthesise outcome data and will conduct meta-analysis (if appropriate) in Review Manager 5, using the random-effects model (Review Manager 2014). We will use the generic inverse variance model to analyse count data (rate ratios) and may use it to compare studies that have presented a group difference, or have adjusted analysis only. We will present effect estimates, with 95% confidence intervals and associated I^2 statistic and P value, for all pooled synthesis. For dichotomous outcomes, if statistical evidence of an effect is reported we will calculate an associated number needed to treat for an additional beneficial outcome (with associated 95% confidence intervals).

Subgroup analysis and investigation of heterogeneity

We plan the following subgroup analyses.

- Children versus adults
- Anatomical site e.g. topical corticosteroid applied to sensitive sites (face/genitals) versus other body sites
- Baseline severity of eczema (mild disease versus moderate and severe, as specified in the trial report)

If there is substantial statistical heterogeneity (via forest plot inspection and using the I^2 statistic), additional clinical and methodological differences will be investigated. Clinical differences may

include filaggrin (FLG) mutation status, age sub-groups of children (0 to 4, 5 to 11, and 11+ years), chronic versus acute disease, and body surface area affected.

Sensitivity analysis

If possible, we will perform a sensitivity analysis removing studies at high risk of bias from the meta-analysis. We will also perform sensitivity analyses where assumptions have been made or data imputed.

'Summary of findings' tables and GRADE assessments

We will create 'Summary of findings' tables for our main comparisons. We have selected the following four most relevant and important comparisons, from both clinician and patient perspectives, to be included in the 'Summary of findings' tables.

1. Proactive versus reactive topical corticosteroid treatment (e.g. twice per week versus 'as required')
2. Frequency of application of topical corticosteroid (e.g. once daily versus twice daily)
3. Duration of use of topical corticosteroids for induction of remission (e.g. short term versus long term)
4. Different potencies of topical corticosteroids (e.g. mild versus moderate; stepping up or stepping down topical corticosteroids)

We will include both primary outcomes and secondary outcomes in each 'Summary of findings' table. We will use the GRADE approach to assess the certainty of evidence for each primary and secondary outcome for our main comparisons. GRADE includes the assessment of five factors: study limitations (risk of bias); inconsistency of results; indirectness of evidence; imprecision; and publication bias (Schünemann 2013). Each outcome can be downgraded by one or two levels for each domain, and we will class the overall certainty as high, moderate, low or very low. We will use GRADEpro to create our 'Summary of findings' tables and undertake our GRADE assessments (GRADEpro GDT).

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* Indicates the major publication for the study

APPENDICES

Appendix I. Draft MEDLINE (Ovid) search strategy

1. exp Eczema/ or eczema\$.ti,ab.
2. exp Dermatitis, Atopic/
3. neurodermatitis.ti,ab. or exp Neurodermatitis/
4. exp Dermatitis/ or dermatitis.ti,ab.
5. besnier\$ prurigo.ti,ab.
6. prurigo diathesique.ti,ab.
7. or/1-6
8. (topical\$ adj3 corticosteroid\$.ti,ab.
9. (topical\$ adj3 steroid\$.ti,ab.
10. (topical\$ adj3 corticoid\$.ti,ab.
11. (topical\$ adj3 glucocorticoid\$.ti,ab.
12. exp Desonide/
13. desonide.mp.
14. alclometasone.mp.
15. amcinonide.mp.
16. exp Beclomethasone/
17. (beclometasone or beclomethasone).mp.
18. exp Betamethasone/
19. Betamethasone.mp.
20. budesonide.mp. or exp Budesonide/
21. clobetasol\$.mp. or exp Clobetasol/
22. clobetasone\$.mp.
23. clocortolone.mp.
24. (exp Cortisone/ or cortisone.ti,ab.) and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
25. Deprodone.mp.
26. desoximetasone.mp. or exp Desoximetasone/
27. exp Dexamethasone/ or dexamethasone.mp.
28. dichlorisone.mp.

29. diflorasone.mp.
 30. exp Diflucortolone/ or diflucortolone.mp.
 31. Difluprednate.mp.
 32. fluclorolone.mp.
 33. Flucloronide.mp.
 34. Fludrocortisone.mp.
 35. fludroxycortide.mp.
 36. (flumetasone or flumethasone).mp.
 37. exp Flumethasone/
 38. fluocinolone.mp.
 39. fluocinonide.mp. or exp Fluocinonide/
 40. fluocortin.mp.
 41. exp Fluocortolone/
 42. fluocortolone.mp.
 43. Fluorometholone.mp.
 44. fluprednidene.mp.
 45. flurandrenolide.mp.
 46. flurandrenolone.mp. or exp Flurandrenolone/
 47. fluticasone.mp.
 48. halcinonide.mp. or exp Halcinonide/
 49. halobetasol.mp.
 50. halometasone.mp.
 51. exp Hydrocortisone/
 52. cortisol.ti,ab. and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
 53. hydrocortisone\$.mp.
 54. (masipredone or Mazipredone).mp.
 55. exp Methylprednisolone/
 56. methylprednisolone.mp.
 57. mometasone.mp.
 58. prednicarbat\$.mp.
 59. exp Prednisolone/
 60. (Prednisolone or prednisone).mp.
 61. ulobetasol.mp.
 62. triamcinolone.mp. or exp Triamcinolone/
 63. exp Adrenal Cortex Hormones/ and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
 64. exp Glucocorticoids/ and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
 65. or/8-64
 66. randomized controlled trial.pt.
 67. controlled clinical trial.pt.
 68. randomized.ab.
 69. placebo.ab.
 70. clinical trials as topic.sh.
 71. randomly.ab.
 72. trial.ti.
 73. 66 or 67 or 68 or 69 or 70 or 71 or 72
 74. exp animals/ not humans.sh.
 75. 73 not 74
 76. 7 and 65 and 75
- [Lines 66-75: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

CONTRIBUTIONS OF AUTHORS

JRC was the contact person with the editorial base.

JRC, EA, and JH co-ordinated the contributions from the co-authors and wrote the final draft of the protocol.

JRC, EA, JH, and BC worked on the Methods section.

JRC, EA, and JH drafted the clinical sections of the Background and responded to the clinical comments of the referees.

JRC, EA, JH, and BC responded to the methodology and statistics comments of the referees.

All authors contributed to writing the protocol.

AR and AA were the consumer co-authors and checked the protocol for readability and clarity. They also ensured that the outcomes are relevant to consumers.

DECLARATIONS OF INTEREST

JRC: member of the HOME executive, ECO co-applicant

EA: none known

JH: none known

KST: member of the HOME executive, ECO joint-lead-applicant

MS: none known

HCW: Chair of the HOME executive, Developed the POEM scale, ECO co-applicant

BC: none known

SL: ECO co-applicant, Honorarium Thorton Ross - lecture

MR: funded by National Institute for Health Research (NIHR) Post-doctoral Fellowship (PDF-2014-07-013)

SML: funded by Wellcome Senior Clinical fellowship

CML: none known.

SP: Merck, FDC & GSK-Stiefel (who produce products that may be used in atopic eczema) are advertisers in the Indian Journal of Dermatology, Venereology & Leprology of which I am the Editor-in-Chief.

PC: none known.

AR: ECO co-applicant

AA: ECO co-applicant

IM: ECO co-applicant

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- NIHR, UK.

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