How has long term control been captured in randomised controlled trials of eczema treatments? A systematic review protocol

Trial team: Sebastien Barbarot, Katrina Abuabara, Helene Aubert, Jo Chalmers, Carsten Flohr, Jon Hanifin, Luigi Naldi, David Margolis, Carle Paul, , Natasha Rogers, , Matthew Ridd, Marie-Louise Schuttelaar, Eric Simpson, Marie Tauber, Annika Volke, Stephan Weidinger, Andreas Wollenberg, Kim S Thomas (Centre of Evidence Based Dermatology University of Nottingham).

Background

The multi-professional Harmonising Outcome Measures for Eczema (HOME) Initiative aims to standardize and validate outcome measurements for eczema[1]. International consensus has defined four criteria as core outcome domain to be assessed in all future eczema trials: eczema signs, eczema symptoms, quality of life and long-term control of flares [2]. A systematic review of flares definitions has been published recently [3] and two validation studies are on-going as part of the HOME initiative. However, capturing eczema flares could only represent *one aspect* of long term control assessment. Indeed, some patients have poor control without any flares. For these patients, long term control can't be captured by a flare outcome. Moreover, capturing flares raises a number of practical issues [3]. Thus, it may be more relevant to assess long term control by using a *disease control outcome measure* rather than a *flare outcome measure*. In asthma, a recent systematic review and expert recommendations stated that the term "asthma exacerbation" should be clearly distinguished from the term "uncontrolled asthma" and that these two dimensions should be assessed by different outcome measures [4]. There has been no systematic review to know how long term control has been captured in eczema trials.

Aims

To identify and qualitatively review how *long term control* has been captured in eczema treatment RCTs published from 2000 onwards.

This will help to provide an evidence based data to inform an international consensus agreement on how to standardize the assessment of long term control in future eczema trials

Specifically we will assess:

Outcomes

Primary

The type of data that have been used to assess 'long term control' in eczema treatment RCTs published from 2000 onwards and which are present in the GREAT database. Long term control can

be captured in many ways, including flare / relapse, use of eczema medication, well controlled weeks , repeated measures of disease severity or other types of data.

Secondary

1. How long term control has been defined in published RCTs on treatments for eczema?
2. Whether a validated (or previously published) scale was used to capture long term control
3. How long term control data has been analysed and reported?
4. Were there any discrepancies between the number of planned data collection points and the number of data collection points really collected and analysed?
5. What is the proportion of published RCTs on treatments for eczema that included long term control as a primary or secondary outcome?
6. What is the proportion of published RCTs that included patient-reported long term control assessment versus investigator-reported?
7. How the outcome measures used to assess long term control met the OMERACT filter of "feasibility"?
8. What is the size of the trials in which long term control has been assessed?
9.

Methods

The GREAT database will be searched to identify RCTs with duration of 3 months or more. The GREAT database (www.greatdatabase.org.uk) contains records of all RCTs of treatments for established eczema published since the inception of the MEDLINE (1966) and EMBASE (1980), the Cochrane Library and the Skin Group Specialised Register databases plus the CINHAL, AMED and LILACS databases from year 2000 onwards. However, this review will only include trials published since 2000 because data extraction, including which outcomes have been used, has only been completed for this subset of trials and prior to this time, most eczema trials were of relatively short duration[5].

Eligibility of trial reports

Trials that include at least one outcome addressing *long term* control will be included. Long term control outcomes are defined as those that provide data over ≥ 3 months, and which include data from a minimum of 3 time points.

This review focuses on clinical outcome only and will not collect information on non-clinical parameters such as biomarkers and barrier function tests.

RCTs will be excluded if they do not include clinical outcomes or if the report is a conference abstract.

No language restrictions will be used.

Data will be extracted for each outcome that provides data at ≥3 time points.

Search Strategy for the GREAT Database

For selection of trials to be included in the GREAT database, the following inclusion criteria were applied:

- Randomised
- have a comparator
- The participants have eczema (usually referred to as atopic eczema or atopic dermatitis) diagnosed by a physician or according to the Hanifin and Rajka criteria or UK working party criteria (or criteria which are very close to these).
- One or more efficacy outcome reported
- The interventions are meant to confer beneficial effects to the person with eczema.

The search strategy used to identify RCTs in the GREAT database is:

MEDLINE (2000 onwards)
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5
10. (animals not (humans and animals)).sh.
11. 9 not 10
12. exp Dermatitis, Atopic/
13. atopic dermatitis.mp.
14. atopic eczema.mp.
15. exp NEURODERMATITIS/
16. neurodermatits.mp.
17. infantile eczema.mp.
18. childhood eczema.mp.
19. Besniers' Prurigo.mp.
20. exp Eczema/ or eczema.mp.
21. 17 or 12 or 20 or 15 or 14 or 18 or 13 or 16 or 19
22. 11 and 21

EMBASE (2000 onwards)
1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp.
6. (singl$ adj blind$).mp.
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp Dermatitis, Atopic/
15. atopic dermatitis.mp.
16. atopic eczema.mp.
17. exp NEURODERMATITIS/
18. neurodermatitis.mp.
19. infantile eczema.mp.
20. childhood eczema.mp.
21. (besnier$ and prurigo).mp.
22. eczema.mp. or exp Eczema/
23. 21 or 17 or 20 or 15 or 14 or 22 or 18 or 16 or 19
24. 23 and 13

Analysis

The outcome measures identified will be summarised qualitatively and discussed.

A subsequent systematic review will be conducted to assess the validation of the long term control outcome measures identified here.

References

1. Schmitt J, Williams H, Group HD: Harmonising Outcome Measures for Eczema (HOME). Report from the First International Consensus Meeting (HOME 1), 24 July 2010, Munich, Germany. *The British* journal *of dermatology* 2010, 163(6):1166-1168.

2. Schmitt J, Langan S, Stamm T, Williams HC, Harmonizing Outcome Measurements in Eczema Delphi p: Core outcome domains for controlled trials and clinical recordkeeping in eczema: international multiperspective Delphi consensus process. *The Journal of investigative dermatology* 2011, 131(3):623-630.

3. Langan SM, Schmitt J, Williams HC, Smith S, Thomas KS: How are eczema "flares" defined? A systematic review and recommendation for future studies. *The British journal of dermatology* 2013.

4. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Jr., Gern J, Heymann PW, Martinez FD, Mauger D, Teague WG *et al*: Asthma outcomes: exacerbations. *The Journal of allergy and clinical immunology* 2012, 129(3 Suppl):S34-48.

5. Hoare C, Li Wan Po A, Williams H: Systematic review of treatments for atopic eczema. *Health technology assessment* 2000, 4(37):1-191.

Appendix 1

Location in HOME Roadmap

	Stage 1 →	Stage 2 →	Stage 3 →			Stage 4 →	S
Task	**Identify all instruments** previously used to measure the domain.	Establish the **extent and quality of testing** of the identified instruments.	Determine **which instruments** are good enough quality **meet the requirements of the OMERACT filter** and be shortlisted for further consideration.			Carry out **validation studies** on shortlisted scales.	Fi ou do
Methodology	Systematic review of outcome instruments used. 	Systematic review of validation studies of the long-list of identified instruments. Highlight any gaps in validation. 	**Apply OMERACT filter;** Truth, discrimination and feasibility:			Consensus discussion and voting to determine what validation studies will be conducted on short-listed instruments. Gaps in testing were highlighted in stage 2 (systematic review). Appropriate methods used to fill the gaps in validation.	Re Ol th co st Co di on be
			Truth *"Is the measure truthful, does it measure what it intends to measure? Is the result unbiased and relevant?"*	**Discrimination** *"Does the measure discriminate between situations that are of interest?"*	**Feasibility** *"Can the measure be applied easily in it's intended setting, given constraints of time, money, and interpretability?"*		
			Consensus discussion and voting on truth: 1. Face validity 2. Content validity 3. Construct validity 4. Criterion validity	Consensus discussion and voting on discrimination: 1. Reliability 2. Sensitivity to change	Consensus discussion and voting on feasibility: 1. Time taken 2. Cost 3. Interpretability 		
Output	**Long-list of all instruments previously used to measure the domain.**	**Summary of which instruments have been tested and the quality, extent and results of any testing.**	**Short-list of potential instruments that meet the requirements of the OMERACT filter.**			**Short-list of fully tested instruments.**	Re ou do

Appendix 2

Proposed data extraction items

Trial	Size	
	Age of participants	
	Duration (in weeks)	Treatment
		Follow-up
	Comments	
Long term Outcomes	Number of outcome measures with ≥ 3 data points	
Use of standard medication	Is it an outcome?	
	Primary/secondary	
	Type of outcome Measure	
	Graph	
	Comments	
Data on flares	Definition	
	Primary/secondary	
	Method of analysis	
	Graph	
	Comments	
Outcome Measure 1	Name of scale	
	Reported by	
	Number of data collection points	Number collected (results)
		Number included in the analysis
		Frequency
		Method of collection
		Comment
	Analysis 1	Description
		Category of analysis
		Primary/Secondary
		Graph
		Comment

	Analysis 2	Description
		Category of analysis
		Primary/Secondary
		Graph
		Comment
	Analysis 3	Description
		Category of analysis
		Primary/Secondary
		Graph
		Comment