National Institute for Health and Care Excellence

Consultation

# Atopic eczema in under 12s: diagnosis and management

## [A] Evidence reviews for adding bath emollients to the management of atopic eczema in children under 12 years

*NICE guideline CG57*

*Evidence reviews underpinning recommendations 1.5.1.4 and 1.5.1.10 to 1.5.1.12*

*March 2023*

*Draft for Consultation*

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ISBN:

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# 1 Adding bath emollients to the standard management of atopic eczema in children under 12 years

## 1.1 Review question

What is the clinical and cost effectiveness of adding bath emollients (bath additives) to the management of atopic eczema in children and young people?

### 1.1.1 Introduction

Currently, NICE's CG57 guideline recommends that emollients are used every day for moisturising, washing, and bathing in children with eczema of all severities. During development of the guideline, there was a lack of good quality evidence around the use of emollients in children with eczema. However, the committee agreed that emollients are important for restoring the defective skin barrier, and that bath and other emollient wash products provide an essential method to clean the skin without the damaging effect of soap and water. To address the lack of evidence around emollients, the committee drafted research recommendations around the effectiveness and cost-effectiveness of emollients.

In 2018, results from the BATHE randomised controlled trial (RCT) were published, which triggered the update of recommendations around the use of bath emollients in NICE CG57. The BATHE trial found that overall, bath emollients are not effective or cost effective in children with eczema. Additionally in March 2018, guidance from NHS England recommended that CCGs should not routinely offer emollient prescriptions for contact dermatitis and mild dry skin. However, there are exceptions, such as for treatment of long-term conditions, or where the patient has not responded to an over-the-counter product. During the NICE surveillance process, topic experts suggested that GP prescriptions of bath emollient products are now being limited in some geographical areas. This review aimed to consider the full evidence base around the effectiveness and cost-effectiveness of bath emollients in children with atopic eczema, and the PICOS is provided in Table 1.

### 1.1.2 Summary of the protocol

**Table 1: PICOS inclusion criteria**

| | |
|---|---|
| Population | Inclusion: Children under 12 with active atopic eczema<br>Exclusion: Children with well-controlled eczema for the last 12 months<br><br>Well-controlled eczema is defined as:<br>• a history of eczema but no current evidence of inflammatory skin disease<br>• less than 1 week of flare a month, or below 5 on the Nottingham Eczema Scale, or not needing any active treatment in the last month. |
| Interventions | Inclusion: Eczema care in combination with regular bath emollients. Bath emollients are defined as oils or emulsifiers (or both) that are added to bath water.<br>Exclusion:<br>• Emollient creams and ointments (such as leave-on emollients that are applied to the skin and left to soak in) |

| | |
|---|---|
| | • Emollient soap substitutes (such as emollients that are used instead of soap) |
| Comparator | Eczema care without bath emollients |
| Outcomes | Primary outcomes:<br>• Difference in eczema severity based on validated measures such as POEM index (Patient Oriented Eczema Measure), Eczema Area and Severity Index (EASI), Itch Severity Scale, NRS-11 for peak itch over the past 24 hours, or SCORAD index (SCORing Atopic Dermatitis)<br>• Number of eczema exacerbations<br>• Overall measure of eczema control based on validated measures, such as Recap of Atopic Eczema (RECAP) and the Atopic dermatitis control tool (ADCT)<br>• Disease-specific quality of life for children (such as the Children's Dermatology Life Quality Index [CDLQI] and the Infants' Dermatitis Quality of Life Index [IDQOL])<br>• Disease-specific quality of life for parents and carers (such as the Dermatitis Family Impact [DFI])<br>• Generic measures of quality of life for children (such as the Child Health Utility Instrument [CHU9D] and the EQ-5D-Y)<br>• Generic quality of life for parents and carers (such as the EQ-5D or SF-36)<br>• Adverse events<br>• Resource use and cost<br>Secondary outcomes:<br>• Treatment adherence<br>• Patient satisfaction<br>• Parent and carer satisfaction<br><br>Data will be collected at the following timepoints:<br>• Short term: up to 6 months<br>• Medium term: between 6 to 12 months<br>• Long term: 12 months and above |
| Study type | • Randomised controlled trials (RCTs)<br>• Systematic reviews of RCTs<br><br>If insufficient evidence is found, we will look at:<br>• Cohort studies (that have been adjusted for confounding factors using an appropriate method for example one of the methods specified in NICE TSD 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal). Key confounders include ethnic group, topical corticosteroid use, and soap substitute use. |

1 For the full protocol see appendix A.

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### 1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and in appendix L.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

#### 1.1.3.1 Search methods

The searches for the clinical effectiveness evidence were run on 08 12 2022. The following databases were searched: CINAHL (Ebsco), Cochrane Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Emcare (Ovid), Epistemonikos, HTA (INAHTA) and MEDLINE ALL (Ovid). Full search strategies for each database are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 08 12 2022. The following databases were searched: EconLit (Ovid), Embase (Ovid), HTA (INAHTA), MEDLINE ALL (Ovid) and NHS Economic Evaluations Database (CRD). Full search strategies for each database are provided in Appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

### 1.1.4 Effectiveness evidence

#### 1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 1061 references (see appendix B for the literature search strategy). An additional 5 references were identified from other sources, such as the previous guideline, committee feedback, and from systematic reviews. Following deduplication there were 529 references.

These 529 references were screened at title and abstract level against the review protocol, with 505 excluded at this level. 47% of references were screened separately by two reviewers with 96% agreement. Discrepancies were resolved by discussion.

The full texts of 12 RCTs, 5 cohort studies, 6 systematic reviews, 1 commentary article were ordered for closer inspection. 3 of these records, corresponding to 2 studies met the criteria specified in the review protocol (appendix A). For a summary of the 2 included studies see Table 2.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

#### 1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

### 1.1.5 Summary of studies included in the effectiveness evidence

**Table 2: Summary of studies included in the effectiveness evidence**

| Study details | Setting/Location/Funding | Population | Intervention | Comparison | Risk of bias |
|---|---|---|---|---|---|
| Santer 2018a<br>N=483<br>Study type: RCT<br>Follow up time: 52 weeks<br><br>Secondary publication: Santer 2018b | Setting: General practices<br>Location: UK<br>Funding source: NIHR | Children aged 1 to 11 years fulfilling UK diagnostic criteria for atopic dermatitis | Bath emollients to be used regularly for 12 months alongside standard eczema management. | Participants were asked not to use bath additives for 12 months and continue with standard eczema care. | Moderate<br><br>*Low for outcome of number of exacerbations* |
| White 1994<br>N=9 participants (18 arms)<br>Study type: non-randomised within-patient left-right side (arm) comparison<br>Follow up time: 4 weeks | Setting: Paediatric outpatient department<br>Location: Scotland<br>Funding source: not reported | Children aged 5 months to 13 years with chronic stable atopic dermatitis. | Daily 15-minute soaking of arm in a basin of warm water with added emollient for 4 weeks alongside standardised therapy. | Standardised therapy only. | Low |

NIHR, National Institute for Health and Care Research; RCT – randomised controlled trial

See appendix D for full evidence tables.

## 1.1.6 Summary of the effectiveness evidence

### Table 3: Summary of effectiveness evidence for eczema severity

**Usual care with bath emollients compared to usual care with no bath emollients**

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** bath emollients **Comparison:** no bath emollients

**Outcomes:** Eczema severity

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| | **Risk with no bath emollients** | **Risk with bath emollients** | | | | |
| **Eczema severity** | | | | | | |
| Eczema severity – mean score over 16 weeks<br><br>Assessed with POEM [MID 3] | - | MD **0.9 lower** (2 lower to 0.2 higher) | - | 461 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |
| Eczema severity – mean score over 52 weeks<br><br>Assessed with POEM [MID 3] | - | MD **1.1 lower** (2.27 lower to 0.07 higher) | - | 461 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |
| **Eczema severity – baseline severity subgroup analysis** | | | | | | |
| Eczema severity – mean score over 16 weeks – baseline severity subgroup analysis – Mild (0-7)<br><br>Assessed with POEM [MID 3] | - | Adjusted difference **0.7 lower** (1.08 lower to 0.95 higher) | - | 187 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |
| Eczema severity – mean score over 16 weeks – baseline severity subgroup analysis – Moderate (8-16)<br><br>Assessed with POEM [MID 3] | - | Adjusted difference **0.65 higher** (0.45 lower to 1.74 higher) | - | 233 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |

## Usual care with bath emollients compared to usual care with no bath emollients

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** bath emollients **Comparison:** no bath emollients

**Outcomes:** Eczema severity

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| | **Risk with no bath emollients** | **Risk with bath emollients** | | | | |
| Eczema severity – mean score over 16 weeks – baseline severity subgroup analysis – Severe (17-28)<br><br>Assessed with POEM [MID 3] | - | Adjusted difference **1.16 lower** (3.62 lower to 1.32 higher) | - | 62 (1 RCTs)[a] | ⨁⨁◯◯ Low[c] | Could not differentiate |
| **Eczema severity – frequency of bathing at 16 weeks subgroup analysis** | | | | | | |
| Eczema severity – mean score over 16 weeks – frequency of bathing at 16 weeks subgroup analysis – 1 to 4 times/week<br><br>Assessed with POEM [MID 3] | - | Adjusted difference **0.26 lower** (1.38 lower to 0.87 higher) | - | 255 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |
| Eczema severity – mean score over 16 weeks – frequency of bathing at 16 weeks subgroup analysis – 5 or more times/week<br><br>Assessed with POEM [MID 3] | - | Adjusted difference **2.27 higher** (0.63 higher to 3.91 higher) | - | 143 (1 RCTs)[a] | ⨁⨁◯◯ Low[c] | Favours bath emollients[d] |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

1 **Explanations**

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

c. Serious concerns due to carer-reported outcomes without blinding and 95% CIs cross 1 line of the MID

d. Santer 2018a reported that higher adjusted mean difference was better

## Table 4: Summary of effectiveness evidence for quality of life

### Usual care with bath emollients compared to usual care with no bath emollients

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** bath emollients **Comparison:** no bath emollients

**Outcomes:** Quality of life outcomes

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| | **Risk with no bath emollients** | **Risk with bath emollients** | | | | |
| **Generic quality of life** | | | | | | |
| Generic quality of life at 16 weeks<br><br>Assessed with CHU-9D score [MID 0.05] | - | MD **0.02 lower** (0.04 lower to 0.0 higher) | - | 461 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |
| Generic quality of life at 52 weeks<br><br>Assessed with CHU-9D score [MID 0.05] | - | MD **0.01 lower** (0.03 lower to 0.01 higher) | - | 461 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |
| **Disease-specific quality of life** | | | | | | |
| Disease-specific quality of life at 16 weeks<br><br>Assessed with DFI score [MID 4.7] | - | Adjusted difference **0.29 higher** (0.57 lower to 1.14 higher) | - | 461 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |
| Disease-specific quality of life at 52 weeks<br><br>Assessed with DFI score [MID 5.9] | - | Adjusted difference **0.29 lower** (1.36 lower to 0.79 higher) | - | 461 (1 RCTs)[a] | ⨁⨁⨁◯ Moderate[b] | Could not differentiate |

### Usual care with bath emollients compared to usual care with no bath emollients

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** bath emollients **Comparison:** no bath emollients

**Outcomes:** Quality of life outcomes

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| | **Risk with no bath emollients** | **Risk with bath emollients** | | | | |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

## Explanations

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

## Table 5 :Summary of effectiveness evidence for adverse events

### Usual care with bath emollients compared to usual care with no bath emollients

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** bath emollients **Comparison:** no bath emollients

**Outcomes:** Adverse events

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| | **Risk with no bath emollients** | **Risk with bath emollients** | | | | |
| **Adverse events - redness** | | | | | | |
| Adverse events – redness – 16 weeks [MID 0.8-1.25] | 230 per 1,000 | 138 per 1000 (94 to 207) | RR **0.6** (0.41 to 0.9) | 461 (1 RCTs)[a] | ⨁⨁◯◯ Low[b] | Favours bath emollients |

## Usual care with bath emollients compared to usual care with no bath emollients

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** bath emollients **Comparison:** no bath emollients

**Outcomes:** Adverse events

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| | **Risk with no bath emollients** | **Risk with bath emollients** | | | | |
| Adverse events – redness – 52 weeks [MID 0.8-1.25] | 292 per 1,000 | 175 per 1,000 (126 to 245) | RR **0.6** (0.43 to 0.84) | 461 (1 RCTs)[a] | ⨁⨁◯◯ Low[b] | Favours bath emollients |
| **Adverse events - stinging** | | | | | | |
| Adverse events – stinging – 16 weeks [MID 0.8-1.25] | 19 per 1,000 | 16 per 1,000 (4 to 63) | RR **0.83** (0.21 to 3.28) | 461 (1 RCTs)[a] | ⨁◯◯◯ Very low[c] | Could not differentiate |
| Adverse events – stinging – 52 weeks [MID 0.8-1.25] | 19 per 1,000 | 28 per 1,000 (8 to 94) | RR **1.45** (0.43 to 4.89) | 461 (1 RCTs)[a] | ⨁◯◯◯ Very low[c] | Could not differentiate |
| **Adverse events – refusal to bathe** | | | | | | |
| Adverse events – refusal to bathe – 16 weeks [MID 0.8-1.25] | 120 per 1,000 | 84 per 1,000 (48 to 145) | RR **0.7** (0.4 to 1.21) | 461 (1 RCTs)[a] | ⨁⨁◯◯ Low[b] | Could not differentiate |
| Adverse events – refusal to bathe – 52 weeks [MID 0.8-1.25] | 148 per 1,000 | 119 per 1,000 (74 to 190) | RR **0.8** (0.5 to 1.28) | 461 (1 RCTs)[a] | ⨁◯◯◯ Very low[c] | Could not differentiate |
| **Adverse events – slipping in the bath** | | | | | | |
| Adverse events – slipping in the bath – 16 weeks [MID 0.8-1.25] | 249 per 1,000 | 174 per 1,000 (122 to 249) | RR **0.7** (0.49 to 1) | 461 (1 RCTs)[a] | ⨁⨁◯◯ Low[b] | Could not differentiate |

## Usual care with bath emollients compared to usual care with no bath emollients

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** bath emollients **Comparison:** no bath emollients

**Outcomes:** Adverse events

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| | **Risk with no bath emollients** | **Risk with bath emollients** | | | | |
| Adverse events – slipping in the bath – 52 weeks<br>[MID 0.8-1.25] | 301 per 1,000 | 223 per 1,000 (163 to 301) | RR **0.74** (0.54 to 1.0) | 461 (1 RCTs)[a] | ⨁⨁◯◯ Low[b] | Could not differentiate |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

## Explanations

a. Santer 2018a

b. Serious concerns due to carer-reported outcomes without blinding and 95% CIs cross 1 line of the MID

c. Very serious concerns due to carer-reported outcomes without blinding and 95% CI cross both lines of the MID

## Table 6: Summary of effectiveness evidence for eczema severity x extent

### Usual care with bath emollients compared to usual care with no bath emollients

**Patient or population:** Children under 12 with active atopic eczema

**Intervention:** daily bath emollient soaking **Comparison:** untreated arm

**Outcomes:** Eczema severity x extent

| Outcomes | Anticipated absolute effects* (95% CI) Risk with no bath emollients | Anticipated absolute effects* (95% CI) Risk with bath emollients | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Summary of effect |
|---|---|---|---|---|---|---|
| **Eczema severity x extent** | | | | | | |
| Severity x extent – 1 week [MID 1.7] | - | MD **0.33 higher** (1.24 lower to 1.9 higher) | - | 18 (1 observational study)[a] | ⨁◯◯◯ Very low[b] | Could not differentiate |
| Severity x extent – 2 weeks [MID 1.2] | - | MD **1.44 higher** (0.3 higher to 2.58 higher) | - | 18 (1 observational study)[a] | ⨁◯◯◯ Very low[b] | Favours untreated arm |
| Severity x extent – 3 weeks [MID 1.9] | - | MD **1.86 higher** (0.78 higher to 2.94 higher) | - | 18 (1 observational study)[a] | ⨁◯◯◯ Very low[b] | Favours untreated arm |
| Severity x extent – 4 weeks [MID 1.2] | - | MD **1.25 higher** (0.47 lower to 2.97 higher) | - | 18 (1 observational study)[a] | ⨁◯◯◯ Very low[b] | Could not differentiate |
| Severity x extent – mean score over 4 weeks [MID 0.7] | - | MD **0.93 higher** (0.3 higher to 1.56 higher) | - | 18 (1 observational study)[a] | ⨁◯◯◯ Very low[b] | Favours untreated arm |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

## Explanations

a. White 1994

b. Very serious concerns as the comparator arm used bath emollients once a week, outcome measure was not a validated measure, and the 95% CIs crossed one line of the MID

**Table 7: Summary of effectiveness for number of eczema exacerbations - evidence not suitable for GRADE as an effect estimate could not be calculated from median (IQR)**

| Outcome | Study | Number of participants | Median (IQR) | Overall risk of Bias | Applicability as a source of data |
|---|---|---|---|---|---|
| Number of eczema exacerbations resulting in primary care consultation | Santer 2018a | N=461 | Usual care with bath additives: **1(0-2)**<br><br>Usual care with no bath additives: **1(0-3)** | Low | Directly appliable – population, intervention, comparator and outcome match the review protocol |

**Table 8: Summary of effectiveness for adherence - evidence not suitable for GRADE**

| Outcome | Study | Number of participants | No. of events (%) | Overall risk of Bias | Applicability as a source of data |
|---|---|---|---|---|---|
| Adherence – Use of bath additives at 16 weeks | Santer 2018b | N=424 | Usual care with bath additives: every time 172(73.8); >50% of the time 44(18.9); <50% of the time 15(6.4); never 2(0.9)<br><br>Usual care without bath additives: every time 14(7.3); >50% of the time 1(0.5); <50% of the time 9(4.7); never 167(87.4) | Moderate | Directly appliable – population, intervention, comparator and outcome match the review protocol |
| Adherence – Use of bath additives at 52 weeks | Santer 2018b | N=379 | Usual care with bath additives: every time 118(58.1); >50% of the time 55(27.1); <50% of the time 20(9.9); never 10(4.9)<br><br>Usual care without bath additives: every time 9(5.1); >50% of the time 4(2.3); <50% | Moderate | Directly appliable – population, intervention, comparator and outcome match the review protocol |

| | | | | | |
|---|---|---|---|---|---|
| | | | of the time 18(10.2); never 145(82.4) | | |
| Adherence – number of baths at 16 weeks | Santer 2018b | N=397 | Usual care with bath additives: 1-2 baths/ week 70(31.7); 3-4 baths/ week 74(33.5); 5-6 baths/ week 45(20.4); ≥7 baths/ week 32(14.5)<br><br>Usual care without bath additives: 1-2 baths/ week 54(30.7); 3-4 baths/ week 56(31.8); 5-6 baths/ week 39(22.2); ≥7 baths/ week 27(15.3) | Moderate | Directly appliable – population, intervention, comparator and outcome match the review protocol |
| Adherence – number of baths at 52 weeks | Santer 2018b | N=379 | Usual care with bath additives: 1-2 baths/ week 69(36.5); 3-4 baths/ week 65(34.4); 5-6 baths/ week 28(14.8); ≥7 baths/ week 27(14.3)<br><br>Usual care without bath additives: 1-2 baths/ week 57(35.6); 3-4 baths/ week 50(31.3); 5-6 baths/ week 29(18.1); ≥7 baths/ week 24(15.0) | Moderate | Directly appliable – population, intervention, comparator and outcome match the review protocol |

**Explanations**

a. Concerns due to carer-reported outcomes without blinding

See appendix F for full GRADE tables.

### 1.1.7 Economic evidence

A search was performed to identify economic evidence for the review question, with 92 papers identified. Following an initial review of titles and abstracts, two papers (Santer et al. 2018b and Lee et al. 2015) were selected for screening on full text, one of which(Santer et al. 2018b) was identified as an applicable economic analysis for the review question; details of this study are summarised in section 1.1.8. The study selection is shown in more detail in Appendix G, while full economic evidence tables along with the checklists for study applicability and study limitations are shown in Appendix H.

#### 1.1.7.1 Included studies

Following full text screening only one study was found to be applicable as economic evidence. The included paper from Santer et al. (2018b) is a RCT that included an economic evaluation alongside. For more details on the economic evidence study selection please see Appendix G and for the economic evidence table please see Appendix H.

#### 1.1.7.2 Excluded studies

One study was excluded at full text review. The excluded studies are summarised in Appendix J.

### 1.1.8 Summary of included economic evidence

**Table 9: Economic evidence profile**

| Study | Applicability | Limitations | Other comments | Incremental | | | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | Cost[a] (£) | Effects (QALYs) | ICER (£/QALY) | |
| Santer et al. 2018b | Directly Applicable | Minor Limitations | Study uses a statistical multi-level regression model used in main clinical study, rather than a decision-analytic model. Results were estimated for time points at 16 and 52 weeks. The population was for children aged between 12 months and 12 years fulfilling the UK Diagnostic Criteria for Atopic Eczema using bath emollients on top of usual eczema care compared to no bath emollients in 52 weeks. | CSRI (excluding intervention costs)<br>16 weeks: -£20.80 (–£38.64 to –£2.95)<br><br>52 Weeks: -£28.85 (–£78.58 to £20.88)<br><br>GP NR (including intervention costs)<br>52 weeks: £14.38 (–£33.45 to £62.21) | 16 weeks: 0.00 (0.00 to 0.00)<br><br>52 weeks: 0.00 (–0.02 to 0.02) | **NA** | Standard economic sensitivity analyses (i.e PSA) were not conducted. The authors did model two alternative sources of resource use (CSRI and GP NR records). These were derived from the multi-level model controlling for baseline Patient Oriented Eczema Measure (POEM). The analysis including intervention costs found no difference in QALYs, therefore cost was the determining factor with authors concluding bath emollients were not cost effective.<br>Cost was also the determining factor in the CSRI analysis, and |

[a] *Study included two different sources of resource use. CSRI = Client service receipt inventory, GP NR = GP notes review.*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | these results found bath emollients to be cost saving. However, this analysis did not include intervention costs; when intervention costs were included in the GP NR analysis results were not cost effective.<br>The authors did conduct further non-reference case sensitivity analysis on patient borne costs. Bath emollients were not cost effective at each time point. |

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### 1.1.9 Economic model

No original economic model was developed for this guideline.

### 1.1.10 The committee's discussion and interpretation of the evidence

#### 1.1.10.1. The outcomes that matter most

The primary outcomes of eczema severity, disease-specific quality of life, generic quality of life, number of eczema exacerbations, overall measure of eczema control, and adverse events were considered, by the committee, to be most important for decision making. The secondary outcomes of treatment adherence, patient satisfaction, and parent and carer satisfaction, while useful, were considered as less important.

There was evidence for the primary outcomes of eczema severity, disease-specific quality of life, generic quality of life, number of eczema exacerbations, and adverse events (including slipping in bath, redness, refusing to bathe, and stinging), and the secondary outcome of treatment adherence from Santer 2018a. These outcomes were generally measured over 16 and 52 weeks. There was also evidence for the outcome of severity x extent from 1 to 4 weeks (White 1994).

There was no evidence for the primary outcome of overall measure of eczema control, and no evidence for the secondary outcomes of patient satisfaction and parent and carer satisfaction.

#### 1.1.10.2 The quality of the evidence

The committee discussed that the BATHE trial (Santer 2018a) was a well-conducted trial and was highly relevant to the review question. The committee felt that that the quality of evidence from the BATHE trial was sufficient that they could make a strong 'do not offer' recommendation. The primary outcomes of eczema severity, disease specific quality of life, and generic quality of life were of moderate quality according to GRADE and were downgraded one level due to risk of bias (carer-reported outcomes without blinding). The evidence for adverse event outcomes was assessed as either low or very low quality due to risk of bias and imprecision. For the subgroup analyses according to baseline severity and number of baths per week, the quality was assessed as either moderate due to risk of bias, or low due to risk of bias and imprecision. Santer 2018a did also caution that subgroup analyses were exploratory only, as they were not adequately powered to identify subgroup differences.

There were some outcomes where it was not possible to assess the quality using GRADE. These included the number of eczema exacerbations, as it was unclear how relative risk could be calculated for a continuous outcome, and therefore only the median and interquartile ranges could be extracted. This outcome was deemed to be at low risk of bias and was directly applicable to the review question. The secondary outcome of treatment adherence was judged as being of moderate risk of bias (carer-reported outcome without blinding). However, this outcome was also not assessed by GRADE as these data were only extracted to provide information on treatment adherence rather than effect.

The outcomes of eczema severity x extent at all timepoints from White 1994 were of very low quality as assessed by GRADE due to imprecision and indirectness (the comparator arm used bath emollients once a week, and the outcome was not a validated measure). In White 1994, outcomes were measured repeatedly over a short space of time (every week for 4 weeks), and additionally a mean score over this period was presented.

The BATHE trial had a longer follow-up period than White 1994, and participants received the intervention for 52 weeks in BATHE compared to only 4 weeks in White 1994. White 1994 had a sample size of only 9 participants, and the committee did not discuss the findings of this study. The committee judged the BATHE trial to be of higher quality and relevance, meaning that it was more important for decision making.

#### 1.1.10.3 Benefits and harms

The BATHE trial found it likely that bath emollients have no effect on eczema severity, disease-specific quality of life, and generic quality of life. Therefore, the committee decided to draft a 'do not offer' recommendation for the use of bath emollients, as the NICE manual states that this is appropriate where good-quality clinical evidence shows a lack of efficacy or effectiveness of an intervention.

There was some evidence that bath emollients may slightly improve eczema severity in patients who bathe 5 or more times a week. However, this outcome was assessed as low quality according to GRADE, and the trial authors cautioned that the findings of subgroup analyses were only exploratory as the BATHE study was not adequately powered to detect subgroup differences. The committee discussed that frequent bathing even without bath emollients may be effective in reducing eczema severity as cleaning would reduce bacteria on the skin. Although it is worth noting that treatment adherence data indicated that the numbers of participants bathing 5 or more times a week were similar in the intervention and comparator arm, and in the no bath additives group eczema severity was slightly more severe in the patients who bathed 5 or more times a week compared with patients who bathed 1 to 4 times per week (mean(SD) POEM score 8.75(6.12) vs 8.00(5.82) respectively).

Evidence from the BATHE trial suggests that bath emollients do not increase the risk of adverse events. However, the committee discussed that acquiring and using bath emollients places an extra burden on patients and carers, and if they are not effective, then it would be beneficial for patients not to use them. This further supports the drafting of a 'do not offer' recommendation.

The committee discussed that although the BATHE trial showed that bath emollients are not likely to be effective at a population level, there will be individual patients who benefit from bath emollients. They discussed that it would be difficult to stop prescribing bath emollients to patients already using bath emollients, especially where there did appear to be some benefit. The committee also discussed how patients may enjoy using bath additives. There were discussions around whether it should be recommended that bath additive prescriptions are limited to secondary care. However, there were concerns that this would lead to unnecessary increases in secondary care referrals. The committee agreed that it would be important to explain to patients that the evidence suggests that bath emollients are not effective, but there is no evidence that bath emollients are harmful, and that they can continue to use bath emollients if they are willing to purchase them over the counter. Consequently, a recommendation was drafted to reflect this discussion. The committee did not see this as an equality issue as overall the evidence has found that bath emollients are not likely to be effective, and therefore it is unlikely that any groups would be disadvantaged. The lay committee members felt that patients would accept not being prescribed bath emollients if the rationale was discussed with them.

The committee discussed that bath emollients may be useful for children with sensory processing disorders, as they may not be able to tolerate the use of leave-on emollients. The committee discussed that bath emollients may be preferable in this population. The committee discussed that both intervention and comparator arms in the BATHE trial used leave-on emollients. Therefore, the effectiveness of bath emollients is unclear when leave-on emollients are not also used. The committee discussed that it is possible to add leave-on

emollients to the bath water by diluting them in hot water, and that advising patients and carers to do this would mean that patients with sensory processing disorders are not adversely affected by the 'do not offer' recommendation.

#### 1.1.10.4 Cost effectiveness and resource use

The committee discussed the evidence from the economic evaluation accompanying the BATHE trial (Santer 2018b). Based on the appraisals checklist for economic evidence (Developing NICE guidelines: the manual, Appendix H), the committee noted that the evidence was directly applicable with minor limitations.

The BATHE economic evaluation used a multi-level regression model to estimate differences in costs and quality of life between study arms. The committee were aware that the model structure differed from decision analytic models typically used in economic evaluation but were satisfied that the model approach was robust for estimating cost effectiveness over the trial period and suitable for decision making.

Quality of life in the study was estimated using CHU-9D, consistent with NICE methods on estimating quality of life in children and young people (NICE health technology evaluations: the manual, Section 4.3.14). Unit costs were taken from the NHS Reference Costs 2015-16 and Unit Costs of Health and Social Care 2016. Two alternative sources of resource use were estimated: the Client Service Receipt Inventory (CSRI) questionnaire adapted for the BATHE trial and a GP notes review (GP NR). The CSRI questionnaire asked carers about resource use relating to the child's eczema at baseline, 16 weeks and 52 weeks. The CSRI focused on resource use arising from accessing services, such as the mean number of GP or dermatology appointments. The GP NR estimated eczema-related resource use based on a review of GP electronic patient records at 52 weeks. The GP NR was used to estimate the costs of bath additives and the associated prescriptions whereas the CSRI only estimated downstream costs and did not estimate intervention costs. For this reason, the committee based their decision on the cost-effectiveness estimates from the GP NR analysis as this best represented the costs borne by the NHS. This is in line with methods outlined in Section 7.3 of Developing NICE guidelines: the manual, which states that all relevant NHS and PSS costs that change as a result of an intervention should be taken into account.

The study concluded that there was no significant difference in quality of life between the bath additive and no bath additive arms with a mean QALY difference of 0.00 (95% CI: -0.01 to 0.02). The estimated mean costs to the NHS at 52 weeks were £180.50 in the bath additive arm and £166.12 in the no bath additive arm. Because the QALY difference between arms was zero an ICER could not be calculated, but the results indicate that bath additives are not cost effective when compared to no bath additives. The committee were aware that several of the estimates had broad confidence intervals and that the mean difference in costs was not statistically significant. However, because the intervention cost more but did not demonstrate clinical effectiveness or generate quality of life gains, the committee concluded that bath additives were unlikely to be a cost effective use of NHS resources in children with eczema under 12. The CRSI estimated costs of consultations, which did not include the intervention costs, were higher in the no bath additive arm at 52 weeks (£126.83 compared to £98.45 in the bath additive arm) although this difference was not significant. From this, the committee considered that bath additives may reduce the number of consultations required over 52 weeks, but that any cost savings generated through this were offset by the cost of the intervention (estimated as £51.88 over 52 weeks).

Having concluded that bath additives were not cost effective for the population, the committee discussed whether to remove mentions of bath additives from the existing recommendations or whether to make an explicit 'do not offer' recommendation. The committee considered prescribing data for bath additives across integrated care boards (ICB)

over time. The prescribing data was taken from the website openprescribing.net and included any prescriptions of drugs labelled as a bath emollient or bath additive. The data showed that although prescriptions for bath additives were decreasing over time, there was still regional variation in prescribing across ICBs. In October 2022, the spending on bath additives ranged from £727 to £26,725 between ICBs. The committee were concerned that simply removing the mention of bath additives could lead to a continuation of regional variation in prescribing and preferred to make an explicit 'do not' recommendation.

The committee deliberated over whether the negative recommendation should be limited to initiation of use ('do not initiate') or all use ('do not offer'). The committee considered the NHS England advice issued to commissioners around items that should not routinely be prescribed in primary care (NHS 2019), which recommends that bath and shower preparations should not be initiated for new patients. Clinicians on the committee advised that there may be a substantial spend on bath additives even when they are not included on formularies, and suggested that this was due to repeat prescriptions for patients already using bath additives. On balance, the committee preferred to make a 'do not offer' recommendation on the basis that bath additives were not a good use of NHS resources and that their withdrawal was unlikely to have a detrimental effect on patient outcomes.

The committee considered whether a negative recommendation might disadvantage patients who were currently using bath additives and felt they were beneficial. The committee were aware that the BATHE economic evaluation had also included a non-reference case analysis which included patient-borne costs, and that the results remained non-cost effective. The committee considered that individuals who wish to continue using bath additives would still have the option of buying them over-the-counter, and that this was consistent with other examples of safe treatments that were not provided on the NHS. As the decision was based on evidence of bath additives lacking efficacy (rather than a lack of evidence of efficacy), the committee were satisfied that this did not represent an equalities issue.

#### 1.1.10.5 Other factors the committee took into account

The committee discussed variations in prescribing of bath emollients across the country, and that a 'do not offer' recommendation from NICE would support guidance from NHS England and would further reduce prescribing and the variation that is currently present.

The committee discussed how antimicrobial bath additives were out of the scope of the guideline, and that it may be appropriate to cross-reference to the Secondary bacterial infection of eczema and other common skin conditions: antimicrobial prescribing guideline (NG190). However, there were concerns that this may increase prescribing of antimicrobial bath additives as a way of providing patients with bath additives if they feel that they are effective.

There was some discussion around how bath emollients are defined in the recommendation. The committee discussed whether it would be appropriate to state the ingredients in bath emollients to add clarity to the recommendation. However, there were concerns that this may date the guideline if new products became available. The committee explained that there are three types of emollients: liquid bath emollients that are generally added to bath water using a cap; leave on emollients that are applied directly to the skin (these can also be diluted in hot water and added to bath water); and emollient products that are marketed as wash products. The committee agreed to use the term 'emollient bath additives' to provide clarity to users.

Finally the CG57 Atopic eczema in under 12s guideline identified a research gap in the effectiveness of emollient bath additives in managing eczema which was addressed by the

BATHE trial. Therefore, the committee agreed that further research was not needed, and they did not make any research recommendations.

### 1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1.4, and 1.5.1.10 to 1.5.1.12.

### 1.1.12 References – included studies

#### 1.1.12.1 Effectiveness

Santer, M., Ridd, M.J., Francis, N.A. et al. (2018a) Emollient bath additives for the treatment of childhood eczema (BATHE): Multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness. BMJ (Online) 361: k1332

Santer M, Rumsby K, Ridd MJ, et al. (2018b) Adding emollient bath additives to standard eczema management for children with eczema: the BATHE RCT. Health Technol Assess. 22(57):1-116. doi:10.3310/hta22570

White MI; Batten TL; Omerod AD (1994) Adverse effects of a daily bathing routine on children with atopic dermatitis. Journal of Dermatological Treatment 4: 21-23

#### 1.1.12.2 Economic

Lee B, W, Detzel P, R. (2015) Treatment of Childhood Atopic Dermatitis and Economic Burden of Illness in Asia Pacific Countries. Annals of Nutrition and Metabolism 66(suppl 1):18-24

Santer M, Rumsby K, Ridd MJ, et al. (2018b) Adding emollient bath additives to standard eczema management for children with eczema: the BATHE RCT. Health Technol Assess. 22(57):1-116. doi:10.3310/hta22570

### 1.1.13 References – other

NHS England (2019) Items which should not routinely be prescribed in primary care: Guidance for CCGs

# Appendices

## Appendix A – Review protocols

**Table 10: Review protocol for adding bath emollients to the management of atopic eczema in children and young people**

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | CRD42022385458 |
| 1. | Review title | The clinical and cost effectiveness of adding bath emollients (bath additives) to the management of atopic eczema in children and young people. |
| 2. | Review question | What is the clinical and cost effectiveness of adding bath emollients (bath additives) to the management of atopic eczema in children and young people? |
| 3. | Objective | To determine whether adding bath emollients (bath additives) to the management of atopic eczema in children and young people is clinically and cost effective. |
| 4. | Searches | **Database searches**<br><br>The principal search strategy will be developed in MEDLINE (Ovid interface) and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. The following databases will be searched:<br><br>• CINAHL<br>• Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley |

| | | |
|---|---|---|
| | | • Cochrane Database of Systematic Reviews (CDSR) via Wiley<br>• EconLit via Ovid<br>• Epistemonikos<br>• Embase via Ovid<br>• EMCARE via Ovid<br>• International HTA Database via INAHTA https://database.inahta.org/<br>• MEDLINE ALL (including In-Process and Epub-Ahead-of-Print) via Ovid<br><br>**Database search limits**<br>Database functionality will be used, where available, to exclude:<br>• animal studies<br>• editorials, letters and commentaries<br>• non-English language studies<br><br>Sources will be searched from 01 March 2007 to the current date. Search filters are not anticipated to be used for specific study types except for economic filters in Embase and Medline.<br><br>The full search strategies will be published in the final review. |
| 5. | Condition or domain being studied | Atopic eczema |
| 6. | Population | Inclusion: Children under 12 with active atopic eczema |

| | | |
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| | | Exclusion: Children with well-controlled eczema for the last 12 months<br><br>Well-controlled eczema is defined as:<br>• a history of eczema but no current evidence of inflammatory skin disease<br>• less than 1 week of flare a month, or below 5 on the Nottingham Eczema Scale, or not needing any active treatment in the last month. |
| 7. | Intervention/Exposure/Test | Inclusion: Eczema care in combination with regular bath emollients. Bath emollients are defined as oils or emulsifiers (or both) that are added to bath water.<br><br>Exclusion:<br>• Emollient creams and ointments (such as leave-on emollients that are applied to the skin and left to soak in)<br>• Emollient soap substitutes (such as emollients that are used instead of soap) |
| 8. | Comparator/Reference standard/Confounding factors | Eczema care without bath emollients |
| 9. | Types of study to be included | • Randomised controlled trials (RCTs)<br>• Systematic reviews of RCTs<br><br>If insufficient evidence is found, we will look at:<br>• Cohort studies (that have been adjusted for confounding factors using an appropriate |

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| | | method for example one of the methods specified in NICE TSD 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal). Key confounders include ethnic group, topical corticosteroid use, and soap substitute use. |
| 10. | Other exclusion criteria | • Articles not published in English<br>• Conference abstracts<br>• Articles not published in peer-reviewed journals |
| 11. | Context | NICE's guideline on Atopic Eczema under 12s (CG57) currently recommends that healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing, and bathing. However, recent published evidence from an NIHR funded trial: Adding emollient bath additives to standard eczema management for children with eczema: the BATHE RCT, indicates that there is no added clinical or economic benefit of using emollient bath additives in children with eczema.<br><br>The review question in the original guideline "What types of emollients are available for atopic eczema in children, how effective are they, what quantities should be used, and how often should they be used?" was modified to specifically address whether bath emollients are effective, reflecting the area in which new evidence was identified. |
| 12. | Primary outcomes | • Difference in eczema severity based on validated measures such as POEM index |

| | | |
|---|---|---|
| | (critical outcomes) | (Patient Oriented Eczema Measure), Eczema Area and Severity Index (EASI), Itch Severity Scale, NRS-11 for peak itch over the past 24 hours, or SCORAD index (SCORing Atopic Dermatitis)<br>• Number of eczema exacerbations<br>• Overall measure of eczema control based on validated measures, such as Recap of Atopic Eczema (RECAP) and the Atopic dermatitis control tool (ADCT)<br>• Disease-specific quality of life for children (such as the Children's Dermatology Life Quality Index [CDLQI] and the Infants' Dermatitis Quality of Life Index [IDQOL])<br>• Disease-specific quality of life for parents and carers (such as the Dermatitis Family Impact [DFI])<br>• Generic measures of quality of life for children (such as the Child Health Utility Instrument [CHU9D] and the EQ-5D-Y)<br>• Generic quality of life for parents and carers (such as the EQ-5D or SF-36)<br>• Adverse events<br>• Resource use and cost<br><br>Data will be collected at the following timepoints:<br>• Short term: up to 6 months<br>• Medium term: between 6 to 12 months<br>• Long term: 12 months and above |
| 13. | Secondary outcomes (important outcomes) | • Treatment adherence<br>• Patient satisfaction<br>• Parent and carer satisfaction |

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| | | Data will be collected at the following timepoints:<br>• Short term: up to 6 months<br>• Medium term: between 6 to 12 months<br>• Long term: 12 months and above |
| 14. | Data extraction (selection and coding) | All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br><br>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. |
| 15. | Risk of bias (quality) assessment | Risk of bias for RCTs, systematic reviews, and cohort studies will be assessed using the Cochrane Risk of Bias v.2.0, ROBIS, and ROBINS-I, respectively, as described in Developing NICE guidelines: the manual. |
| 16. | Strategy for data synthesis | Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event.<br><br>A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct |

| | | |
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| | | but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g).<br><br>Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I2≥50%, or where significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis, when random effects models will be used instead.<br><br>Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias.<br><br>GRADE will be used to assess the quality of the outcomes. Outcomes will be rated as high quality initially and downgraded from this point. |
| 17. | Analysis of sub-groups | Where disaggregation possible:<br><br>• Severity of eczema<br>• Frequency of use (based on number of baths per week)<br>• Bath duration<br>• Strength of emollient |
| 18. | Type and method of review | ☒ Intervention<br><br>☐ Diagnostic<br><br>☐ Prognostic<br><br>☐ Qualitative<br><br>☐ Epidemiologic<br><br>☐ Service Delivery<br><br>☐ Other (please specify) |

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| 19. | Language | English | | |
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | December 2022 | | |
| 22. | Anticipated completion date | June 2023 | | |
| 23. | Stage of review at time of this submission | **Review stage** | **Started** | **Completed** |
| | | Preliminary searches | ☐ | ☐ |
| | | Piloting of the study selection process | ☐ | ☐ |
| | | Formal screening of search results against eligibility criteria | ☐ | ☐ |
| | | Data extraction | ☐ | ☐ |
| | | Risk of bias (quality) assessment | ☐ | ☐ |

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| | | Data analysis | ☐ | ☐ |
| 24. | Named contact | **5a. Named contact**<br>NICE Guideline Development Team B<br><br>**5b Named contact e-mail**<br>AtopicDermatitisUnder12@nice.org.uk<br><br>**5e Organisational affiliation of the review**<br>National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team B | | |
| 25. | Review team members | From the NICE Guideline Development Team:<br>• Caroline Mulvihill – technical lead<br>• Sarah Matthews – technical analyst<br>• Lucy Beggs – technical adviser (health economics)<br>• Muna Ali – technical analyst (health economics)<br>• Jemma Deane – information specialist<br>• Adam O'Keefe – project manager | | |
| 26. | Funding sources/sponsor | This systematic review is being completed by the NICE Guideline Development Team which receives funding from NICE. | | |
| 27. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. | | |

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| 28. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10364. |
| 29. | Other registration details | No other registrations of this protocol |
| 30. | Reference/URL for published protocol | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022385458 |
| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 32. | Keywords | Systematic review; eczema; bath emollients; bath additives. |
| 33. | Details of existing review of same topic by same authors | This is a new review that will update recommendations on bath emollients in the 'Treatment' section in NICE guideline CG57: Atopic Eczema in under 12s: diagnosis and management. |
| 34. | Current review status | ☒ Ongoing<br>☐ Completed but not published<br>☐ Completed and published<br>☐ Completed, published and being updated |

| | | |
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| | | ☐ Discontinued |
| 35. | Additional information | This review will be used to update the NICE guideline on Atopic Eczema in under 12s: diagnosis and management. |
| 36. | Details of final publication | www.nice.org.uk |

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# Appendix B – Literature search strategies

**What is the clinical and cost effectiveness of adding bath emollients (bath additives) to the management of atopic eczema in children and young people?**

### Background and development

### Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 08 12 2022. This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

### Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess ‘low-probability’ matches. All decisions made for the review can be accessed via the deduplication history.

### Prior work

The search strategy was based on the terms used in Atopic Eczema in under 12s: diagnosis and management NICE guideline CG57

Modifications were made to the original search strategies for the specifications in the review protocol. No age filters or brand names were required.

### Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude letters, editorials, news and conferences were applied in adherence to standard NICE practice and the review protocol.

The search was limited from 1st March 2007 to 8th December 2022 as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

**Cost effectiveness searches**

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

**Key decisions**

The search strategy was developed to find evidence for the specified population and intervention in the review protocol.

At the scope and protocol QA meeting, it was suggested that there might be potential to expand this work to include a broader update on adults. As numbers retrieved from databases were manageable it was decided not to use an age filter. Adult studies can therefore be tagged for future use.

Searches were translated from Medline to other databases as close as practically possible.

It is noted that 5 additional references have been added by the technical team in the PRISMA flowchart. These were added to EPPI after the database searches were complete. van Zuuren EJ, Fedorowicz Z, Christensen R et al. (2017) Emollients and moisturisers for eczema. Cochrane Database Syst Rev 2: CD012119 was used as a source for primary studies.

**Clinical/public health searches**

**Main search – Databases**

| Database | Date searched | Database Platform | Database segment or version | No. of results downloaded |
|---|---|---|---|---|
| Cochrane Central Register of Controlled Trials (CENTRAL) | 8/12/22 | Wiley | Issue 11 of 12, November 2022 | 122 |
| Cochrane Database of Systematic Reviews (CDSR) | 8/12/22 | Wiley | Issue 12 of 12, December 2022 | 3 |
| Cumulative Index to Nursing and Allied Health Literature (CINAHL) | 8/12/22 | EBSCOhost | - | 19 |
| Embase | 8/12/22 | Ovid | Embase 1974 to 2022 December 07 | 439 |
| Emcare | 8/12/22 | Ovid | Ovid Emcare 1995 to 2022 Week 46 | 92 |
| Epistemonikos | 8/12/22 | Epistemonikos | - | 67 |
| International Health Technology Assessment Database (INAHTA) | 8/12/22 | https://database.inahta.org/ | - | 1 |
| MEDLINE ALL | 8/12/22 | Ovid | Ovid MEDLINE(R) ALL 1946 to December 06, 2022 | 318 |

**Search strategy history**

**Database name: Cochrane (Wiley)**

ID Search Hits

#1 MeSH descriptor: [Eczema] explode all trees 1234
#2 MeSH descriptor: [Dermatitis, Atopic] this term only 2061
#3 (eczema*):ti,ab,kw 4665
#4 (((atopic* or disseminated or endogenous) near/4 (dermatiti* or neurodermatiti*))):ti,ab,kw 5535
#5 ((besnier* NEXT prurigo)):ti,ab,kw 8
#6 {or #1-#5} 7833
#7 MeSH descriptor: [Emollients] this term only 492
#8 MeSH descriptor: [Emulsifying Agents] this term only 14
#9 MeSH descriptor: [Emulsions] this term only 605
#10 ((additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*)):ti,ab,kw 27192
#11 {or #7-#10} 27192
#12 MeSH descriptor: [Baths] this term only 345
#13 ((bath* or shower* or wash* or water or soak*)):ti,ab,kw 72305
#14 {or #12-#13} 72305
#15 #6 and #11 and #14 360
#16 "conference":pt or (clinicaltrials or trialsearch):so 656457
#17 #15 NOT #16 with Cochrane Library publication date Between Mar 2007 and Dec 2022, in Cochrane Reviews, Cochrane Protocols 3
#18 #15 NOT #16 with Publication Year from 2007 to 2022, in Trials 122

**Database name: CINAHL**

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S14 | S6 AND S10 AND S13 | Limiters - Published Date: 20070301-20221231; English Language; Human Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 19 |
| S13 | S11 OR S12 | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 93,767 |
| S12 | TI ( (bath* or shower* or wash* or water or soak*) ) OR AB ( (bath* or shower* or wash* or water or soak*) ) | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 92,439 |

| | | | | |
|---|---|---|---|---|
| S11 | (MH "Bathing and Baths") | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 3,398 |
| S10 | S7 OR S8 OR S9 | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 39,626 |
| S9 | TI ( (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*) ) OR AB ( (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*) ) | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 38,201 |
| S8 | (MH "Emulsions") | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 779 |
| S7 | (MH "Emollients") | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 1,717 |
| S6 | S1 OR S2 OR S3 OR S4 OR S5 | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - | 9,461 |

| | | | | |
|---|---|---|---|---|
| | | | Advanced Search Database - CINAHL | |
| S5 | TI (besnier* N1 prurigo) OR AB (besnier* N1 prurigo) | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 1 |
| S4 | TI ( ((atopic* or disseminated or endogenous) N4 (dermatiti* or neurodermatiti*)) ) OR AB ( ((atopic* or disseminated or endogenous) N4 (dermatiti* or neurodermatiti*)) ) | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 4,183 |
| S3 | TI eczema* OR AB eczema* | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 3,756 |
| S2 | (MH "Dermatitis, Atopic") | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 4,404 |
| S1 | (MH "Eczema") | Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 2,778 |

**Database name: Embase**

1 exp eczema/ (30993)
2 exp atopic dermatitis/ (52773)
3 eczema*.tw. (29862)
4 ((atopic* or disseminated or endogenous) adj4 (dermatiti* or neurodermatiti*)).tw. (40850)
5 besnier* prurigo.tw. (18)
6 or/1-5 (88421)
7 emollient agent/ (7117)
8 emulsifying agent/ (4374)
9 emulsion/ (36050)
10 (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*).tw. (438536)
11 or/7-10 (448699)
12 bath/ (13233)
13 (bath* or shower* or wash* or water or soak*).tw. (1279564)
14 or/12-13 (1282680)
15 6 and 11 and 14 (1062)
16 limit 15 to english language (930)
17 nonhuman/ not (human/ and nonhuman/) (5105900)
18 16 not 17 (876)
19 limit 18 to dc=20070301-20221231 (749)
20 (letter or editorial).pt. (1995082)
21 19 not 20 (740)
22 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5397534)
23 21 not 22 (439)

**Database name: Emcare**

1 exp eczema/ (3796)
2 exp atopic dermatitis/ (4572)
3 eczema*.tw. (3481)
4 ((atopic* or disseminated or endogenous) adj4 (dermatiti* or neurodermatiti*)).tw. (4404)
5 besnier* prurigo.tw. (0)
6 or/1-5 (10496)
7 emollient agent/ (1124)
8 emulsifying agent/ (308)
9 emulsion/ (2932)
10 (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*).tw. (61761)
11 or/7-10 (62828)
12 bath/ (3265)
13 (bath* or shower* or wash* or water or soak*).tw. (158727)
14 or/12-13 (158962)
15 6 and 11 and 14 (115)
16 limit 15 to english language (104)
17 nonhuman/ not (human/ and nonhuman/) (360235)
18 16 not 17 (104)
19 limit 18 to dc=20070301-20221231 (92)

**Database name: Epistemonikos**

(title:(((((atopic* OR disseminated OR endogenous) AND (dermatiti* OR neurodermatiti*)) OR (eczema* OR besnier* prurigo)))) OR abstract:(((((atopic* OR disseminated OR endogenous) AND (dermatiti* OR neurodermatiti*)) OR (eczema* OR besnier* prurigo))))) AND (title:(((additive* OR

bioemulsifi* OR demulcen* OR emollient* OR emulgator* OR emulsi* OR oil* OR moisturi*) AND (bath* OR shower* OR wash* OR water OR soak*))) OR abstract:(((additive* OR bioemulsifi* OR demulcen* OR emollient* OR emulgator* OR emulsi* OR oil* OR moisturi*)))) AND (title:(bath* OR shower* OR wash* OR water OR soak*) OR abstract:(bath* OR shower* OR wash* OR water OR soak*))

67 results with date limits added

**Database name: INAHTA**

| | | | |
|---|---|---|---|
| | 17 | #16 AND #15 | 1 |
| | 16 | * FROM 2007 TO 2022 | 13844 |
| | 15 | #14 AND #11 AND #6 | 3 |
| | 14 | #13 OR #12 | 126 |
| | 13 | (bath* or shower* or wash* or water or soak*) | 125 |
| | 12 | "Baths"[mh] | 11 |
| | 11 | #10 OR #9 OR #8 OR #7 | 41 |
| | 10 | ((additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*)) | 40 |
| | 9 | "Emulsions"[mh] | 1 |
| | 8 | "Emulsifying Agents"[mh] | 0 |
| | 7 | "Emollients"[mh] | 2 |
| | 6 | #5 OR #4 OR #3 OR #2 OR #1 | 49 |
| | 5 | (besnier prurigo) | 0 |
| | 4 | ((atopic* or disseminated or endogenous) ) AND ((dermatiti* or neurodermatiti*)) | 27 |
| | 3 | (eczema*) | 25 |
| | 2 | "Dermatitis, Atopic"[mh] | 38 |
| | 1 | "Eczema"[mhe] | 16 |

**Database name: MEDLINE (ALL)**

1 exp Eczema/ (12489)
2 Dermatitis, Atopic/ (23710)
3 eczema*.tw. (20767)
4 ((atopic* or disseminated or endogenous) adj4 (dermatiti* or neurodermatiti*)).tw. (25723)
5 besnier* prurigo.tw. (48)
6 or/1-5 (50875)
7 Emollients/ (2199)
8 Emulsifying Agents/ (1821)
9 Emulsions/ (21215)
10 (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*).tw. (363123)
11 or/7-10 (368764)
12 Baths/ (5460)
13 (bath* or shower* or wash* or water or soak*).tw. (1094392)
14 or/12-13 (1096065)
15 6 and 11 and 14 (493)
16 limit 15 to english language (453)

17 animals/ not humans/ (5038960)
18 16 not 17 (422)
19 limit 18 to ed=20070301-20221231 (301)
20 limit 18 to dt=20070301-20221231 (331)
21 19 or 20 (334)
22 limit 21 to (letter or historical article or comment or editorial or news or case reports) (16)
23 21 not 22 (318)

### Cost-effectiveness searches

### Main search – Databases

| Database | Date searched | Database Platform | Database segment or version | No. of results downloaded |
|---|---|---|---|---|
| EconLit | 8/12/22 | OVID | Econlit 1886 to November 24, 2022 | 0 |
| Embase | 8/12/22 | Ovid | Embase 1974 to 2022 December 07 | 85 |
| International Health Technology Assessment Database (INAHTA) | 8/12/22 | https://database.inahta.org/ | - | 1 |
| MEDLINE ALL | 8/12/22 | Ovid | Ovid MEDLINE(R) ALL 1946 to December 06, 2022 | 56 |
| NHS Economic Evaluation Database (NHS EED) (legacy database) | 8/12/22 | CRD | - | 0 |

### Search strategy history

### Database name: Econlit

1 eczema*.tw. (5)
2 ((atopic* or disseminated or endogenous) adj4 (dermatiti* or neurodermatiti*)).tw. (3)
3 besnier* prurigo.tw. (0)
4 or/1-3 (7)
5 (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*).tw. (24129)
6 (bath* or shower* or wash* or water or soak*).tw. (20831)

7 4 and 5 and 6 (0)

**Database name: Embase**

1 exp eczema/ (30993)
2 exp atopic dermatitis/ (52773)
3 eczema*.tw. (29862)
4 ((atopic* or disseminated or endogenous) adj4 (dermatiti* or neurodermatiti*)).tw. (40850)
5 besnier* prurigo.tw. (18)
6 or/1-5 (88421)
7 emollient agent/ (7117)
8 emulsifying agent/ (4374)
9 emulsion/ (36050)
10 (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*).tw. (438536)
11 or/7-10 (448699)
12 bath/ (13233)
13 (bath* or shower* or wash* or water or soak*).tw. (1279564)
14 or/12-13 (1282680)
15 6 and 11 and 14 (1062)
16 limit 15 to english language (930)
17 nonhuman/ not (human/ and nonhuman/) (5105900)
18 16 not 17 (876)
19 limit 18 to dc=20070301-20221231 (749)
20 (letter or editorial).pt. (1995082)
21 19 not 20 (740)
22 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5397534)
23 21 not 22 (439)
24 exp Health Economics/ (987289)
25 exp "Health Care Cost"/ (327680)
26 exp Pharmacoeconomics/ (224022)
27 Monte Carlo Method/ (48075)
28 Decision Tree/ (19201)
29 econom$.tw. (462979)
30 cba.tw. (13791)
31 cea.tw. (39761)
32 cua.tw. (1759)
33 markov$.tw. (37388)
34 (monte adj carlo).tw. (57991)
35 (decision adj3 (tree$ or analys$)).tw. (33891)
36 (cost or costs or costing$ or costly or costed).tw. (936579)
37 (price$ or pricing$).tw. (68767)
38 budget$.tw. (45030)
39 expenditure$.tw. (86710)
40 (value adj3 (money or monetary)).tw. (4091)
41 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (9406)
42 or/24-41 (2126210)
43 "Quality of Life"/ (582802)
44 Quality Adjusted Life Year/ (32975)
45 Quality of Life Index/ (3096)
46 Short Form 36/ (36801)
47 Health Status/ (145594)
48 quality of life.tw. (551438)
49 quality adjusted life.tw. (24706)
50 (qaly$ or qald$ or qale$ or qtime$).tw. (25040)

51 disability adjusted life.tw. (5737)
52 daly$.tw. (5514)
53 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (47930)
54 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2815)
55 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (11593)
56 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (68)
57 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (505)
58 (euroqol or euro qol or eq5d or eq 5d).tw. (27861)
59 (qol or hql or hqol or hrqol).tw. (122593)
60 (hye or hyes).tw. (158)
61 health$ year$ equivalent$.tw. (41)
62 utilit$.tw. (353981)
63 (hui or hui1 or hui2 or hui3).tw. (2910)
64 disutili$.tw. (1149)
65 rosser.tw. (138)
66 quality of wellbeing.tw. (68)
67 quality of well-being.tw. (551)
68 qwb.tw. (264)
69 willingness to pay.tw. (11868)
70 standard gamble$.tw. (1174)
71 time trade off.tw. (1963)
72 time tradeoff.tw. (310)
73 tto.tw. (2086)
74 or/43-73 (1216117)
75 cost utility analysis/ (11535)
76 quality adjusted life year/ (32975)
77 cost*.ti. (185342)
78 (cost* adj2 utilit*).tw. (11803)
79 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (359841)
80 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (61556)
81 (qualit* adj2 adjust* adj2 life*).tw. (25306)
82 QALY*.tw. (24786)
83 (incremental* adj2 cost*).tw. (26632)
84 ICER.tw. (11911)
85 utilities.tw. (14122)
86 markov*.tw. (37388)
87 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (67905)
88 ((utility or effective*) adj2 analys*).tw. (35069)
89 (willing* adj2 pay*).tw. (13410)
90 (EQ5D* or EQ-5D*).tw. (23589)
91 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4687)
92 (european* adj2 quality adj3 ("5" or five)).tw. (871)
93 or/75-92 (593632)
94 42 or 74 or 93 (3190432)
95 23 and 94 (85)

**Database name: INAHTA**

| | | | |
|---|---|---|---|
| | 17 | #16 AND #15 | 1 |

| | | | |
|---|---|---|---|
| | 16 | * FROM 2007 TO 2022 | 13844 |
| | 15 | #14 AND #11 AND #6 | 3 |
| | 14 | #13 OR #12 | 126 |
| | 13 | (bath* or shower* or wash* or water or soak*) | 125 |
| | 12 | "Baths"[mh] | 11 |
| | 11 | #10 OR #9 OR #8 OR #7 | 41 |
| | 10 | ((additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*)) | 40 |
| | 9 | "Emulsions"[mh] | 1 |
| | 8 | "Emulsifying Agents"[mh] | 0 |
| | 7 | "Emollients"[mh] | 2 |
| | 6 | #5 OR #4 OR #3 OR #2 OR #1 | 49 |
| | 5 | (besnier prurigo) | 0 |
| | 4 | ((atopic* or disseminated or endogenous) ) AND ((dermatiti* or neurodermatiti*)) | 27 |
| | 3 | (eczema*) | 25 |
| | 2 | "Dermatitis, Atopic"[mh] | 38 |
| | 1 | "Eczema"[mhe] | 16 |

**Database name: MEDLINE ALL**

1 exp Eczema/ (12486)
2 Dermatitis, Atopic/ (23691)
3 eczema*.tw. (20761)
4 ((atopic* or disseminated or endogenous) adj4 (dermatiti* or neurodermatiti*)).tw. (25704)
5 besnier* prurigo.tw. (48)
6 or/1-5 (50853)
7 Emollients/ (2196)
8 Emulsifying Agents/ (1821)
9 Emulsions/ (21212)
10 (additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*).tw. (362987)
11 or/7-10 (368627)
12 Baths/ (5460)
13 (bath* or shower* or wash* or water or soak*).tw. (1094048)
14 or/12-13 (1095721)
15 6 and 11 and 14 (493)
16 limit 15 to english language (453)
17 animals/ not humans/ (5037450)
18 16 not 17 (422)
19 limit 18 to ed=20070301-20221231 (301)
20 limit 18 to dt=20070301-20221231 (331)
21 19 or 20 (334)
22 limit 21 to (letter or historical article or comment or editorial or news or case reports) (16)
23 21 not 22 (318)
24 Economics/ (27478)
25 exp "Costs and Cost Analysis"/ (261509)
26 Economics, Dental/ (1920)
27 exp Economics, Hospital/ (25654)
28 exp Economics, Medical/ (14373)

29 Economics, Nursing/ (4013)
30 Economics, Pharmaceutical/ (3089)
31 Budgets/ (11659)
32 exp Models, Economic/ (16161)
33 Markov Chains/ (15857)
34 Monte Carlo Method/ (31768)
35 Decision Trees/ (12040)
36 econom$.tw. (378751)
37 cba.tw. (10953)
38 cea.tw. (25972)
39 cua.tw. (1390)
40 markov$.tw. (29974)
41 (monte adj carlo).tw. (56495)
42 (decision adj3 (tree$ or analys$)).tw. (24880)
43 (cost or costs or costing$ or costly or costed).tw. (702219)
44 (price$ or pricing$).tw. (50093)
45 budget$.tw. (34220)
46 expenditure$.tw. (66207)
47 (value adj3 (money or monetary)).tw. (3057)
48 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (4417)
49 or/24-48 (1358818)
50 "Quality of Life"/ (255023)
51 quality of life.tw. (350471)
52 "Value of Life"/ (5795)
53 Quality-Adjusted Life Years/ (15250)
54 quality adjusted life.tw. (16310)
55 (qaly$ or qald$ or qale$ or qtime$).tw. (13593)
56 disability adjusted life.tw. (4778)
57 daly$.tw. (4286)
58 Health Status Indicators/ (24075)
59 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (29538)
60 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2520)
61 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (7252)
62 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (38)
63 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (444)
64 (euroqol or euro qol or eq5d or eq 5d).tw. (15363)
65 (qol or hql or hqol or hrqol).tw. (68412)
66 (hye or hyes).tw. (75)
67 health$ year$ equivalent$.tw. (40)
68 utilit$.tw. (254622)
69 (hui or hui1 or hui2 or hui3).tw. (1867)
70 disutili$.tw. (586)
71 rosser.tw. (106)
72 quality of wellbeing.tw. (41)
73 quality of well-being.tw. (470)
74 qwb.tw. (213)
75 willingness to pay.tw. (7866)
76 standard gamble$.tw. (898)
77 time trade off.tw. (1334)
78 time tradeoff.tw. (261)
79 tto.tw. (1314)
80 or/50-79 (710010)
81 Cost-Benefit Analysis/ (91225)
82 Quality-Adjusted Life Years/ (15250)

83 Markov Chains/ (15857)
84 exp Models, Economic/ (16161)
85 cost*.ti. (139013)
86 (cost* adj2 utilit*).tw. (7229)
87 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (259546)
88 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (43729)
89 (qualit* adj2 adjust* adj2 life*).tw. (16655)
90 QALY*.tw. (13447)
91 (incremental* adj2 cost*).tw. (16234)
92 ICER.tw. (5523)
93 utilities.tw. (8839)
94 markov*.tw. (29974)
95 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (51686)
96 ((utility or effective*) adj2 analys*).tw. (23467)
97 (willing* adj2 pay*).tw. (8963)
98 (EQ5D* or EQ-5D*).tw. (12148)
99 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (3452)
100 (european* adj2 quality adj3 ("5" or five)).tw. (628)
101 or/81-100 (473907)
102 49 or 80 or 101 (2003261)
103 23 and 102 (56)

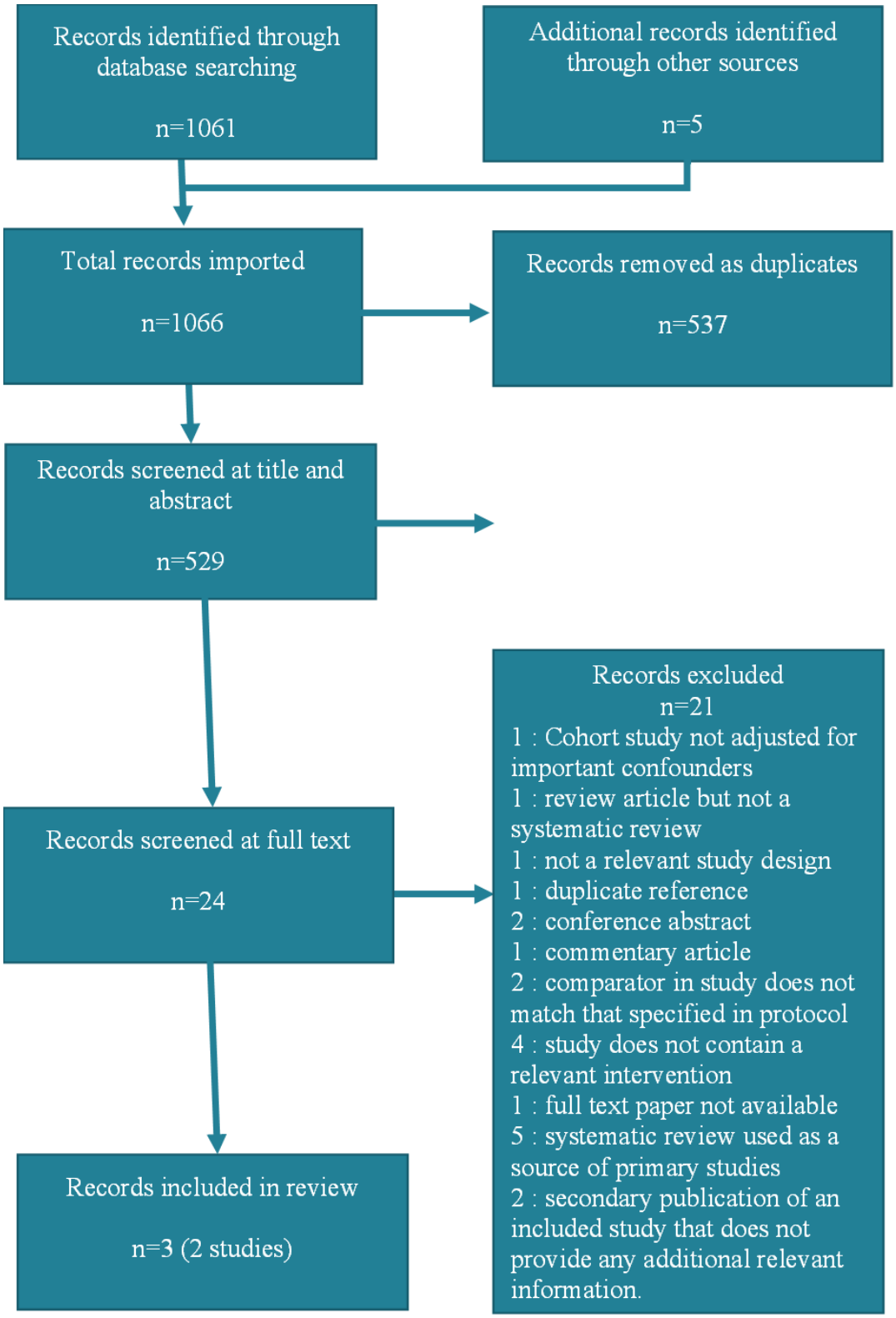
**Database name: NHS EED**

| Line | Search | Hits | | |
|---|---|---|---|---|
| | 1 | MeSH DESCRIPTOR ECZEMA EXPLODE ALL TREES | 26 | Delete |
| | 2 | MeSH DESCRIPTOR Dermatitis, Atopic | 105 | Delete |
| | 3 | (eczema*) | 118 | Delete |
| | 4 | (((atopic* or disseminated or endogenous) NEAR4 (dermatiti* or neurodermatiti*))) | 91 | Delete |
| | 5 | ((besnier* NEAR1 prurigo)) | 0 | Delete |
| | 6 | #1 OR #2 OR #3 OR #4 OR #5 | 187 | Delete |
| | 7 | MeSH DESCRIPTOR Emollients | 15 | Delete |
| | 8 | MeSH DESCRIPTOR Emulsifying Agents | 0 | Delete |
| | 9 | MeSH DESCRIPTOR Emulsions | 15 | Delete |
| | 10 | ((additive* or bioemulsifi* or demulcen* or emollient* or emulgator* or emulsi* or oil* or moisturi*)) | 479 | Delete |
| | 11 | #7 OR #8 OR #9 OR #10 | 479 | Delete |
| | 12 | MeSH DESCRIPTOR Baths | 32 | Delete |
| | 13 | ((bath* or shower* or wash* or water or soak*)) | 1198 | Delete |
| | 14 | #12 OR #13 | 1198 | Delete |
| | 15 | #6 AND #11 AND #14 | 8 | Delete |

*From <https://www.crd.york.ac.uk/CRDWeb/HistoryPage.asp>*
0 in EED

# Appendix C – Effectiveness evidence study selection

**Figure 1: PRISMA flow diagram**



# Appendix D – Effectiveness evidence

### Santer, 2018a

| | |
|---|---|
| **Bibliographic Reference** | Santer, M.; Ridd, M.J.; Francis, N.A.; Stuart, B.; Rumsby, K.; Chorozoglou, M.; Becque, T.; Roberts, A.; Liddiard, L.; Nollett, C.; Hooper, J.; Prude, M.; Wood, W.; Thomas, K.S.; Thomas-Jones, E.; Williams, H.C.; Little, P.; Emollient bath additives for the treatment of childhood eczema (BATHE): Multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness; BMJ (Online); 2018; vol. 361; k1332 |

### Study details

| | |
|---|---|
| **Other publications associated with this study included in review** | Santer, M., Rumsby, K., Ridd, M.J. et al. (2018) Adding emollient bath additives to standard eczema management for children with eczema: The BATHE RCT. Health Technology Assessment 22(57): 1-116<br>Santer, M., Rumsby, K., Ridd, M.J. et al. (2015) Bath additives for the treatment of childhood eczema (BATHE): Protocol for multicentre parallel group randomised trial. BMJ Open 5(10): e009575<br>Stuart, B., Rumsby, K., Santer, M. et al. (2018) Feasibility of weekly participant-reported data collection in a pragmatic randomised controlled trial in primary care: Experiences from the BATHE trial (Bath Additives for the Treatment of cHildhood Eczema). Trials 19(1): 582 |
| **Trial registration number and/or trial name** | ISRCTN84102309 |
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Wales and the west and south of England |
| **Study setting** | 96 general practices |
| **Study dates** | Recruitment took place between November 2014 and May 2016, and 52-week follow-ups were completed in June 2017 |
| **Sources of funding** | National Institute for Health Research (NIHR) Health Technology Assessment Programme<br>NIHR Clinical Research Network Service Support Costs<br>The University of Southampton was the research sponsor for this trial. |
| **Inclusion criteria** | Age<br>1 to 11 years<br>Fulfilled UK Diagnostic Criteria for Atopic Eczema |
| **Exclusion criteria** | Eczema severity - Children with inactive or very mild eczema over the past 12 months (defined as a score of 5 or less on the Nottingham eczema severity scale)<br>Bathing frequency - usually less than once a week<br>Carer not willing to accept randomisation<br>Participating in other trial(s)<br>Other sibling(s) participating in the trial |

| | |
|---|---|
| **Intervention(s)** | Participants we prescribed bath additives by their general practice and were asked to use them regularly for 12 months. Practices were encouraged to issue the three bath additives most commonly prescribed in the UK: Oilatum (63% light liquid paraffin), Balneum (85% soya oil), Aveeno (no summary of product characteristics available). Except for products containing antimicrobials, other bath additives could be issued.<br><br>[Both arms were given standardised written advice on how to wash, including the use of leave-on emollient as a soap substitute. Both groups were advised to continue with standard eczema management, including regular leave-on emollients and topical corticosteroids when required. Ongoing clinical care was otherwise unchanged.] |
| **Comparator** | Participants were not prescribed bath additives and were asked not to use bath additives for 12 months.<br><br>[Both arms were given standardised written advice on how to wash, including the use of leave-on emollient as a soap substitute. Both groups were advised to continue with standard eczema management, including regular leave-on emollients and topical corticosteroids when required. Ongoing clinical care was otherwise unchanged.] |
| **Outcome measures** | Eczema severity - Patient oriented eczema measure (POEM)<br>Number of exacerbations - that resulted in primary care consultation<br>Disease-specific quality of life - Dermatitis family impact (DFI)<br>Generic measure of quality of life - Child health utility-9D (CHU-9D)<br>Adverse events - such as stinging, redness, slipping in the bath, or refusal to bathe (parent or carer report) |
| **Number of participants** | 483 participants were randomised |
| **Duration of follow-up** | Outcomes measured over 16 and 52 weeks |
| **Loss to follow-up** | Bath additive arm: 13 out of 265 participants (4.9%) lost to follow-up<br>No bath additive: 9 out of 218 participants (4.1%) lost to follow-up |
| **Methods of analysis** | Participants were analysed in the group to which they were randomised, regardless of their adherence to that allocation (intention to treat).<br>Per-protocol analyses were also presented, where analyses were carried out on the basis of bath additive use.<br>Sample size calculations were performed for repeated measures analysis of variance in weekly POEM scores over 16 weeks, aiming to detect a mean difference of 2.0 (SD 7.0) points between the two study arms).<br>Primary analysis for the total POEM score was performed using a multilevel mixed model framework with observations over time from weeks 1 to 16 (level 1) nested within participants (level 2). Adjusted results controlled for baseline POEM score, recruiting centre, and any significant confounders including ethnic group, topical corticosteroid use, and soap substitute use. The model used all the observed data and made the assumption that missing POEM scores are missing at random given the observed data.<br>Monthly POEM measure up to one year was analysed using repeated measures analysis in line with analysis of POEM scores over 16 weeks. |

| | |
|---|---|
| | For other secondary outcomes, linear regression was used for continuous outcomes if the assumptions were met. Otherwise, non-parametric analyses were used.<br>Pre-planned sensitivity analyses and exploratory subgroup analyses were performed. |
| **Additional comments** | Subgroup analyses were described as exploratory only, as the trial was not powered to explore the effect in subgroups, and therefore there is a risk of type I errors (a statistically significant result is found due to data having been tested multiple times rather than because a genuine effect exists between the groups).<br>The Santer 2018b HTA reported the weekly mean POEM scores from baseline to 16 weeks, and monthly mean POEM scores from baseline to 52 weeks. Only the mean scores over 16 weeks and 52 weeks were extracted, as these were the main outcomes that were reported in the BMJ papers, and the data were similar across the timepoints. |

### Study arms

### Usual care with bath additive (N = 265)

### Usual care with no bath additive (N = 218)

### Characteristics

### Arm-level characteristics

| Characteristic | Usual care with bath additive (N = 265) | Usual care with no bath additive (N = 218) |
|---|---|---|
| **% Female**<br>Sample size | n = 126 ; % = 48 | n = 118 ; % = 54 |
| **Mean age (SD) Years**<br>Mean (SD) | 5.4 (2.9) | 5.2 (2.9) |
| **White**<br>Sample size | n = 228 ; % = 86 | n = 176 ; % = 82 |
| **Black**<br>Sample size | n = 6 ; % = 2 | n = 9 ; % = 4 |
| **Asian**<br>Sample size | n = 15 ; % = 6 | n = 16 ; % = 7 |
| **Mixed Race**<br>Sample size | n = 10 ; % = 4 | n = 9 |
| **Chinese**<br>Sample size | n = 2 ; % = 1 | n = 3 ; % = 1 |

| Characteristic | Usual care with bath additive (N = 265) | Usual care with no bath additive (N = 218) |
|---|---|---|
| **Other**<br>Sample size | n = 3 ; % = 1 | n = 2 ; % = 1 |
| **Mean POEM score (SD)**<br>**0-28**<br>Mean (SD) | 9.5 (5.7) | 10.1 (5.8) |
| **Mild (0-7)**<br>Sample size | n = 114 ; % = 43 | n = 73 ; % = 33 |
| **Moderate (8-16)**<br>Sample size | n = 119 ; % = 45 | n = 114 ; % = 52 |
| **Severe (17-28)**<br>Sample size | n = 31 ; % = 12 | n = 31 |
| **Median DFI score (IQR)**<br>**0-30**<br>Median (IQR) | 2 (1 to 6) | 3 (1 to 7) |
| **Mean NESS score (SD)**<br>**3-15**<br>Mean (SD) | 9.5 (2.3) | 9.5 (2.3) |
| **Mean CHU-9D score (SD)**<br>**Utility values**<br>Mean (SD) | 0.9 (0.1) | 0.9 (0.1) |

### Outcomes

### Study timepoints

- 16 weeks
- 52 weeks

### Outcome table - Arm based

| Outcome | Usual care with no bath additives, 16 weeks, N = 209 | Usual care with no bath additives, 52 weeks, N = 209 | Usual care with bath additives, 16 weeks, N = 252 | Usual care with bath additives, 52 weeks, N = 252 |
|---|---|---|---|---|
| **Eczema severity Mean POEM score over timepoint**<br>**(0-28)**<br>Mean (SD) | 8.4(6.0) | 8.4(6.4) | 7.5(6.0) | 7.3(6.3) |
| **Generic QoL** | 0.89(0.1) | 0.91(0.1) | 0.91(0.1) | 0.90(0.1) |

| Outcome | Usual care with no bath additives, 16 weeks, N = 209 | Usual care with no bath additives, 52 weeks, N = 209 | Usual care with bath additives, 16 weeks, N = 252 | Usual care with bath additives, 52 weeks, N = 252 |
|---|---|---|---|---|
| **CHU-9D**<br>Mean (SD) | | | | |
| **Adverse events – slipping in bath**<br>No of events (%) | 52(25) | 63(30) | 44(17) | 56(22) |
| **Adverse events – stinging**<br>No of events (%) | 4(2) | 4(2) | 4(2) | 7(3) |
| **Adverse events – redness**<br>No of events (%) | 48(23) | 61(29) | 35(14) | 44(17) |
| **Adverse events – refusal to bathe**<br>No of events (%) | 25(12) | 31(15) | 21(8) | 30(12) |
| **Number of eczema exacerbations**<br>**(resulting in primary care consultation)**<br>Median (IQR)<br><br>Note- although a risk ratio was reported for this outcome, it was unclear how this would be possible for a continuous outcome, and this was not explained in the methods. | - | 1(0-2) | - | 1(0-3) |

Eczema severity - Polarity - Lower values are better
Generic QoL - Polarity - Higher values are better
Adverse events – slipping in bath - Polarity - Lower values are better
Adverse events – stinging - Polarity - Lower values are better
Adverse events – redness - Polarity - Lower values are better
Adverse events – refusal to bath - Polarity - Lower values are better
Number if eczema exacerbations – Polarity - Lower values are better

**Outcome table - Study based table**

| Outcome | Usual care with bath additives vs usual care with no bath additives, 16 weeks, N = 461 | Usual care with bath additives vs usual care with no bath additives, 52 weeks, N = 461 |
|---|---|---|
| **Disease specific QoL**<br>**DFI**<br>**(0-30)** | 0.29(-0.57 to 1.14) | -0.29(-1.36 to 0.79) |

| Outcome | Usual care with bath additives vs usual care with no bath additives, 16 weeks, N = 461 | Usual care with bath additives vs usual care with no bath additives, 52 weeks, N = 461 |
|---|---|---|
| Adjusted difference (95% CI) | | |

Disease specific QoL - Polarity – Lower values are better

**Outcome table for subgroup analysis - Study based**

| Outcome | Usual care with bath additives vs usual care with no bath additives, 16 weeks, N = 461 |
|---|---|
| **Baseline eczema severity – Mild (0-7)**<br><br>**Eczema severity**<br>**Mean POEM score over timepoint (0-28)**<br>Mean (SD) | -0.07(-1.08 to 0.95) |
| **Baseline eczema severity – Moderate (8-16)**<br><br>**Eczema severity**<br>**Mean POEM score over timepoint (0-28)**<br>Mean (SD) | 0.65(-0.45 to 1.74) |
| **Baseline eczema severity – Severe (17-28)**<br><br>**Eczema severity**<br>**Mean POEM score over timepoint (0-28)**<br>Mean (SD) | -1.16(-3.62 to 1.32) |
| **Frequency of bathing at 16 weeks – 1 to 4 times/week**<br><br>**Eczema severity**<br>**Mean POEM score over timepoint (0-28)**<br>Mean (SD) | -0.26(-1.38 to 0.87) |
| **Frequency of bathing at 16 weeks – 5 or more times/week**<br><br>**Eczema severity**<br>**Mean POEM score over timepoint (0-28)**<br>Mean (SD) | 2.27(0.63 to 3.91) |

Eczema severity - Polarity - Lower values are better

**Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)**

| | | |
|---|---|---|
| Overall risk of bias | Medium | Some concerns due to carer-reported outcomes without blinding<br><br>*For the outcome of number of eczema exacerbations, overall risk of bias was low, as this was assessed by reviewing primary care records.* |
| Applicability as a source of data | Directly applicable | Population, intervention, comparator and outcome match the review protocol |

**Santer, 2018b**

| | |
|---|---|
| **Bibliographic Reference** | Santer, M.; Rumsby, K.; Ridd, M.J.; Francis, N.A.; Stuart, B.; Chorozoglou, M.; Roberts, A.; Liddiard, L.; Nollett, C.; Hooper, J.; Prude, M.; Wood, W.; Thomas-Jones, E.; Becque, T.; Thomas, K.S.; Williams, H.C.; Little, P.; Adding emollient bath additives to standard eczema management for children with eczema: The BATHE RCT; Health Technology Assessment; 2018; vol. 22 (no. 57); 1-116 |

**Study details**

| | |
|---|---|
| **Secondary publication of another included study- see primary study for details** | Santer, M.; Ridd, M.J.; Francis, N.A.; Stuart, B.; Rumsby, K.; Chorozoglou, M.; Becque, T.; Roberts, A.; Liddiard, L.; Nollett, C.; Hooper, J.; Prude, M.; Wood, W.; Thomas, K.S.; Thomas-Jones, E.; Williams, H.C.; Little, P.; Emollient bath additives for the treatment of childhood eczema (BATHE): Multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness; BMJ (Online); 2018; vol. 361; k1332 |

**Outcome table – Arm-based**

| Outcome | Usual care with no bath additives, 16 weeks, N = 191 | Usual care with no bath additives, 52 weeks, N = 209 | Usual care with bath additives, 16 weeks, N = 233 | Usual care with bath additives, 52 weeks, N = 252 |
|---|---|---|---|---|
| **Use of bath additive – Every time**<br>No of events (%) | 14 (7.3) | 9 (5.1) | 172 (73.8) | 118 (58.1) |
| **Use of bath additive – More than half of the time**<br>No of events (%) | 1 (0.5) | 4 (2.3) | 44 (18.9) | 55 (27.1) |

| Outcome | Usual care with no bath additives, 16 weeks, N = 191 | Usual care with no bath additives, 52 weeks, N = 209 | Usual care with bath additives, 16 weeks, N = 233 | Usual care with bath additives, 52 weeks, N = 252 |
|---|---|---|---|---|
| **Use of bath additive – Less than half of the time** No of events (%) | 9 (4.7) | 18 (10.2) | 15 (6.4) | 20 (9.9) |
| **Use of bath additive – Never** No of events (%) | 167 (87.4) | 145 (82.4) | 2 (0.9) | 10 (4.9) |

| Outcome | Usual care with no bath additives, 16 weeks, N = 176 | Usual care with no bath additives, 52 weeks, N = 176 | Usual care with bath additives, 16 weeks, N = 221 | Usual care with bath additives, 52 weeks, N = 203 |
|---|---|---|---|---|
| **Number of baths per week – 1 to 2** No of events (%) | 54 (30.7) | 57 (35.6) | 70 (31.7) | 69 (36.5) |
| **Number of baths per week – 3 to 4** No of events (%) | 56 (31.8) | 50 (31.3) | 74 (33.5) | 65 (34.4) |
| **Number of baths per week – 5 to 6** No of events (%) | 39 (22.2) | 29 (18.1) | 45 (20.4) | 28 (14.8) |
| **Number of baths per week – 7 or more** No of events (%) | 27 (15.3) | 24 (15.0) | 32 (14.5) | 27 (14.3) |

**Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Risk of bias judgement | Moderate<br>*(Some concerns due to carer-reported outcomes without blinding)* |
| Overall bias and Directness | Overall Directness | Directly applicable<br>*(Population, intervention, comparator and outcome match the review protocol)* |

## White, 1994

| | |
|---|---|
| **Bibliographic Reference** | White MI; Batten TL; Omerod AD; Adverse effects of a daily bathing routine on children with atopic dermatitis.; Journal of Dermatological Treatment; 1994; vol. 4; 21-23 |

## Study details

| | |
|---|---|
| **Other publications associated with this study included in review** | None |
| **Trial registration number and/or trial name** | Not reported |
| **Study type** | Prospective cohort study<br>within-patient left-right side (arm) comparison |
| **Study location** | Aberdeen, Scotland |
| **Study setting** | Paediatric outpatient department at Royal Aberdeen Children's Hospital |
| **Study dates** | Not reported |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | Chronic stable atopic dermatitis<br>Parents willing to encourage child to comply with study and bring them for weekly review |
| **Exclusion criteria** | Clinical infection<br>Known allergy to the emollient<br>An atopic condition severe enough that it required the child to have systemic corticosteroid therapy |
| **Intervention(s)** | Parents were asked to randomly select one of their child's arms for 15-minute daily soaking for in a basin of warm water with added emollient (1 ml Oilatum - equivalent to bath concentration) for 4 weeks. |

| | |
|---|---|
| | [Both arms - Minor adjustments to the children's routine were advised so that therapy was standardised to weekly bathing in a bath containing 15 ml Oilatum; twice daily application of a moisturiser and topical corticosteroid; use of a 3% aqueous emulsifying wax as a soap substitute. Existing oral antihistamine treatment was not altered, and families were asked to avoid any known aggravating situations or commencing any new activities/therapies that may affect the atopic dermatitis.] |
| **Comparator** | [Both arms - Minor adjustments to the children's routine were advised so that therapy was standardised to weekly bathing in a bath containing 15 ml Oilatum; twice daily application of a moisturiser and topical corticosteroid; use of a 3% aqueous emulsifying wax as a soap substitute. Existing oral antihistamine treatment was not altered, and families were asked to avoid any known aggravating situations or commencing any new activities/therapies that may affect the atopic dermatitis.] |
| **Outcome measures** | Extent and severity of atopic dermatitis on each arm<br>Extent score multiplied by severity score: Extent: 0 =0%, 1 = 1-25%, 2 = 26-50%, 3 = 51-75%, 4 = 76-100%. Severity: 0 = clear, 1 = mild (dry, scaly, erythematous), 2 = moderate (oedema, excoriated papules, crusts), 3 = severe (excoriations, fissuring, lichenification) |
| **Number of participants** | 9 participants (18 arms) |
| **Duration of follow-up** | 4 weeks |
| **Loss to follow-up** | No loss to follow-up reported |
| **Methods of analysis** | • A mean of the clinical score for each arm was averaged over the 4-week period.<br>• The scores approximated a normal distribution. Therefore, a two-tailed paired t-test was used to compare treated and untreated arms and the t confidence interval was used to calculate the 95% confidence intervals. |
| **Additional comments** | The initial severity of both arms was similar. |

### Study arms

### Daily soaked arm (N = 9)

### Daily untreated arm (N = 9)

**Characteristics**

**Study-level characteristics**

| Characteristic | Study (N = 9) |
|---|---|
| **% Female**<br>Sample size | n = 6; % = 66.6 |
| **Age** | Range : 5 months to 13 years |

**Outcomes**

**Study timepoints**

- 1 week
- 2 weeks
- 3 weeks
- 4 weeks
- Mean score over 4 weeks

**Outcome table - Study based table**

| Outcome | Daily soaked arm vs daily untreated arm, 1 week, N = 9 | Daily soaked arm vs daily untreated arm, 2 weeks, N = 9 | Daily soaked arm vs daily untreated arm, 3 weeks, N = 9 | Daily soaked arm vs daily untreated arm, 4 weeks, N = 9 | Daily soaked arm vs daily untreated arm, mean score over 4 weeks, N = 9 |
|---|---|---|---|---|---|
| **Severity x extent** Mean difference (SE) | 0.33(0.80) | 1.44(0.58) | 1.86 (0.55) | 1.25(0.88) | 0.93(0.32) |

Severity x extent - Polarity – Lower values are better

**Critical appraisal - ROBINS-I tool**

| | | |
|---|---|---|
| Overall risk of bias | Low | Confounders listed in the protocol were accounted for due to the study design (left-right comparison). Baseline severity was not accounted for. However, analyses show that baseline severity was similar in both arms. |
| Applicability as a source of data | Indirectly applicable | The comparator arm used bath emollients once a week, and the outcome measure was not a validated measure. |

# Appendix E – Forest plots

Forest plots have not been reported as it was not possible to perform any meta-analysis and only single-study analyses were carried out.

# Appendix F – GRADE tables

**Table 11: GRADE - eczema severity**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bath emollient | No bath emollient | Relative (95% CI) | Absolute (95% CI) | |
| **Eczema severity mean score over 16 weeks – POEM score [MID 3 points]; Better indicated by lower values** | | | | | | | | | | | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | - | **MD 0.9 lower** (2 lower to 0.2 higher) | ⊕⊕⊕◯ MODERATE |
| **Eczema severity mean score over 52 weeks – POEM score [MID 3 points]; Better indicated by lower values** | | | | | | | | | | | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | - | **MD 1.1 lower** (2.27 lower to 0.07 higher) | ⊕⊕⊕◯ MODERATE |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

### Explanations

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

c. Not applicable as single-study analysis

d. No concerns as population, intervention, comparator, and outcomes match the review protocol

e. No concerns as 95% CIs do not cross any lines of the MID

**Table 12: GRADE - Eczema severity – baseline severity subgroup analysis**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bath emollient | No bath emollient | Relative (95% CI) | Absolute (95% CI) | |
| **Eczema severity - mean score over 16 weeks – baseline severity subgroup analysis - Mild (0-7) - POEM score – [MID 3 points]; Better indicated by higher values** | | | | | | | | | | | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | - | **Adjusted difference 0.7 lower** (1.08 lower to 0.95 higher) | ⨁⨁⨁◯ MODERATE |

**Eczema severity - mean score over 16 weeks – baseline severity subgroup analysis - Moderate (8-16) - POEM score – [MID 3 points]; Better indicated by higher values**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | **-** | **Adjusted difference 0.65 higher** (0.45 lower to 1.74 higher) | ⊕⊕⊕◯ MODERATE |

**Eczema severity - mean score over 16 weeks – baseline severity subgroup analysis - Severe (17-28) - POEM score – [MID 3 points]; Better indicated by higher values**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | serious[f] | none | 252 | 209 | - | **Adjusted difference 1.16 lower** (3.62 lower to 1.32 higher) | ⊕⊕◯◯ LOW |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

### Explanations

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

c. Not applicable as single-study analysis

d. No concerns as population, intervention, comparator, and outcomes match the review protocol

e. No concerns as 95% CIs do not cross any lines of the MID

f. Serious concerns as 95% Cis cross one line of the MID

**Table 13 - GRADE - Eczema severity – frequency of bathing at 16 weeks subgroup analysis**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bath emollient | No bath emollient | Relative (95% CI) | Absolute (95% CI) | |
| **Eczema severity - mean score over 16 weeks – frequency of bathing at 16 weeks subgroup analysis – 1 to 4 times/week - POEM score – [MID 3 points]; Better indicated by higher values** | | | | | | | | | | | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | - | **Adjusted difference 0.26 lower** (1.38 lower to 0.87 higher) | ⨁⨁⨁◯ MODERATE |
| **Eczema severity - mean score over 16 weeks – frequency of bathing at 16 weeks subgroup analysis -5 or more times/week - POEM score – [MID 3 points]; Better indicated by higher values** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | serious[f] | none | 252 | 209 | - | **Adjusted difference 2.27 higher** (0.63 higher to 3.91 higher) | ⊕⊕◯◯ LOW |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## Explanations

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

c. Not applicable as single-study analysis

d. No concerns as population, intervention, comparator, and outcomes match the review protocol

e. No concerns as 95% CIs do not cross any lines of the MID

f. Serious concerns as 95% Cis cross one line of the MID

**Table 14: GRADE - Generic quality of life**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bath emollient | No bath emollient | Relative (95% CI) | Absolute (95% CI) | |
| **Generic quality of life at 16 weeks – CHU-9D score [MID 0.05 points]; Better indicated by higher values** | | | | | | | | | | | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | - | **MD 0.02 lower** (0.04 lower to 0.0 higher) | ⊕⊕⊕◯ MODERATE |
| **Generic quality of life at 52 weeks – CHU-9D score [MID 0.05 points]; Better indicated by higher values** | | | | | | | | | | | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | **-** | **MD 0.01 lower** (0.03 lower to 0.01 higher) | ⊕⊕⊕◯ MODERATE |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## Explanations

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

c. Not applicable as single-study analysis

d. No concerns as population, intervention, comparator, and outcomes match the review protocol

e. No concerns as 95% CIs do not cross any lines of the MID

**Table 15: GRADE - Disease-specific quality of life**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bath emollient | No bath emollient | Relative (95% CI) | Absolute (95% CI) | |
| **Disease-specific quality of life at 16 weeks – DFI score [MID 4.7 points]; Better indicated by lower values** | | | | | | | | | | | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | - | **Adjusted difference 0.29 higher** (0.57 lower to 1.14 higher) | ⨁⨁⨁◯ MODERATE |
| **Disease-specific quality of life at 52 weeks – DFI score [MID 5.9 points]; Better indicated by lower values** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | 252 | 209 | - | **Adjusted difference 0.29 lower** (1.36 lower to 0.79 higher) | ⊕⊕⊕◯ MODERATE |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

### Explanations

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

c. Not applicable as single-study analysis

d. No concerns as population, intervention, comparator, and outcomes match the review protocol

e. No concerns as 95% Cis do not cross any lines of the MID

### Table 16: GRADE - Adverse events

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bath emollient | No bath emollient | Relative (95% CI) | Absolute (95% CI) | |
| **Adverse events - redness - 16 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient** | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bath emollient | No bath emollient | Relative (95% CI) | Absolute (95% CI) | |
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | serious[e] | none | 35/252 (13.9%) | 48/209 (23%) | **RR 0.6** (0.41 to 0.9) | **92 fewer per 1,000** (from 23 fewer to 136 fewer) | ⨁⨁◯◯ LOW |

**Adverse events – redness – 52 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | serious[e] | none | 44/252 (17.5%) | 61/209 (29.2%) | **RR 0.6** (0.43 to 0.84) | **117 fewer per 1,000** (from 47 fewer to 166 fewer) | ⨁⨁◯◯ LOW |

**Adverse events - stinging - 16 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | very serious[f] | none | 4/252 (1.6%) | 4/209 (1.9%) | **RR 0.83** (0.21 to 3.28) | **3 fewer per 1,000** (from 15 fewer to 44 more) | ⊕◯◯◯ VERY LOW |

**Adverse events – stinging – 52 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | very serious[f] | none | 7/252 (2.8%) | 4/209 (1.9%) | **RR 1.45** (0.43 to 4.89) | **9 more per 1,000** (from 11 fewer to 74 more) | ⊕◯◯◯ VERY LOW |

**Adverse events – refusal to bathe - 16 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | serious[g] | none | 21/252 (8.3%) | 25/209 (12%) | **RR 0.7** (0.4 to 1.21) | **36 fewer per 1,000** (from 72 fewer to 25 more) | ⊕⊕◯◯ LOW |

**Adverse events – refusal to bathe – 52 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | very serious[f] | none | 30/252 (11.9%) | 31/209 (14.8) | **RR 0.8** (0.5 to 1.28) | **30 fewer per 1,000** (from 74 fewer to 42 more) | ⊕◯◯◯ VERY LOW |

**Adverse events – slipping in bath - 16 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | serious[g] | none | 44/252 (17.5%) | 52/209 (24.9%) | **RR 0.7** (0.49 to 1) | **75 fewer per 1,000** (from 127 fewer to 0 more) | ⊕⊕◯◯ LOW |

**Adverse events – slipping in bath – 52 weeks [MID 0.8 to 1.25]; RRs greater than 1 favour no bath emollient**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | randomised trials | serious[b] | not serious[c] | not serious[d] | Serious[g] | none | 56/252 (22.2%) | 63/209 (30.1%) | **RR 7.4 (0.54 to 1.0)** | **78 fewer per 1,000** (from 139 fewer to 0 more) | ⊕⊕◯◯ LOW |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

### Explanations

a. Santer 2018a

b. Some concerns due to carer-reported outcomes without blinding

c. Not applicable as single-study analysis

d. No concerns as population, intervention, comparator, and outcomes match the review protocol

e. Some concerns as 95% CIs cross one line of the MID

f. Very serious concerns as 95% Cis cross 2 lines of the MID

g. Serious concerns as 95% Cis cross 1 line of the MID

**Table 17: GRADE - Severity x extent**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Daily bath emollient soaking | Untreated arm | Relative (95% CI) | Absolute (95% CI) | |
| **Severity x extent - 1 week [MID 1.7]; Better indicated by lower values** | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Daily bath emollient soaking | Untreated arm | Relative (95% CI) | Absolute (95% CI) | |
| 1[a] | observational studies | not serious[b] | not serious[c] | very serious[d] | serious[e] | none | 9 | 9 | - | **MD 0.33 higher** (1.24 lower to 1.9 higher) | ⊕◯◯◯ VERY LOW |

**Severity x extent - 2 weeks [MID 1.2]; Better indicated by lower values**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | observational studies | not serious[b] | not serious[c] | very serious[d] | serious[e] | none | 9 | 9 | - | **MD 1.44 higher** (0.3 higher to 2.58 higher) | ⊕◯◯◯ VERY LOW |

**Severity x extent - 3 weeks [MID 1.2]; Better indicated by lower values**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | observational studies | not serious[b] | not serious[c] | very serious[d] | serious[e] | none | 9 | 9 | - | **MD 1.86 higher** (0.78 higher to 2.94 higher) | ⊕◯◯◯ VERY LOW |

**Severity x extent - 4 weeks [MID 1.9]; Better indicated by lower values**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | observational studies | not serious[b] | not serious[c] | very serious[d] | serious[e] | none | 9 | 9 | - | **MD 1.25 higher** (0.47 lower to 2.97 higher) | ⊕◯◯◯ VERY LOW |

**Severity x extent – mean score over 4 weeks [MID 0.7]; Better indicated by lower values**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | observational studies | not serious[b] | not serious[c] | very serious[d] | serious[e] | none | 9 | 9 | - | **MD 0.93 higher** (0.3 higher to 1.56 higher) | ⊕◯◯◯ VERY LOW |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

### Explanations

a. White 1994

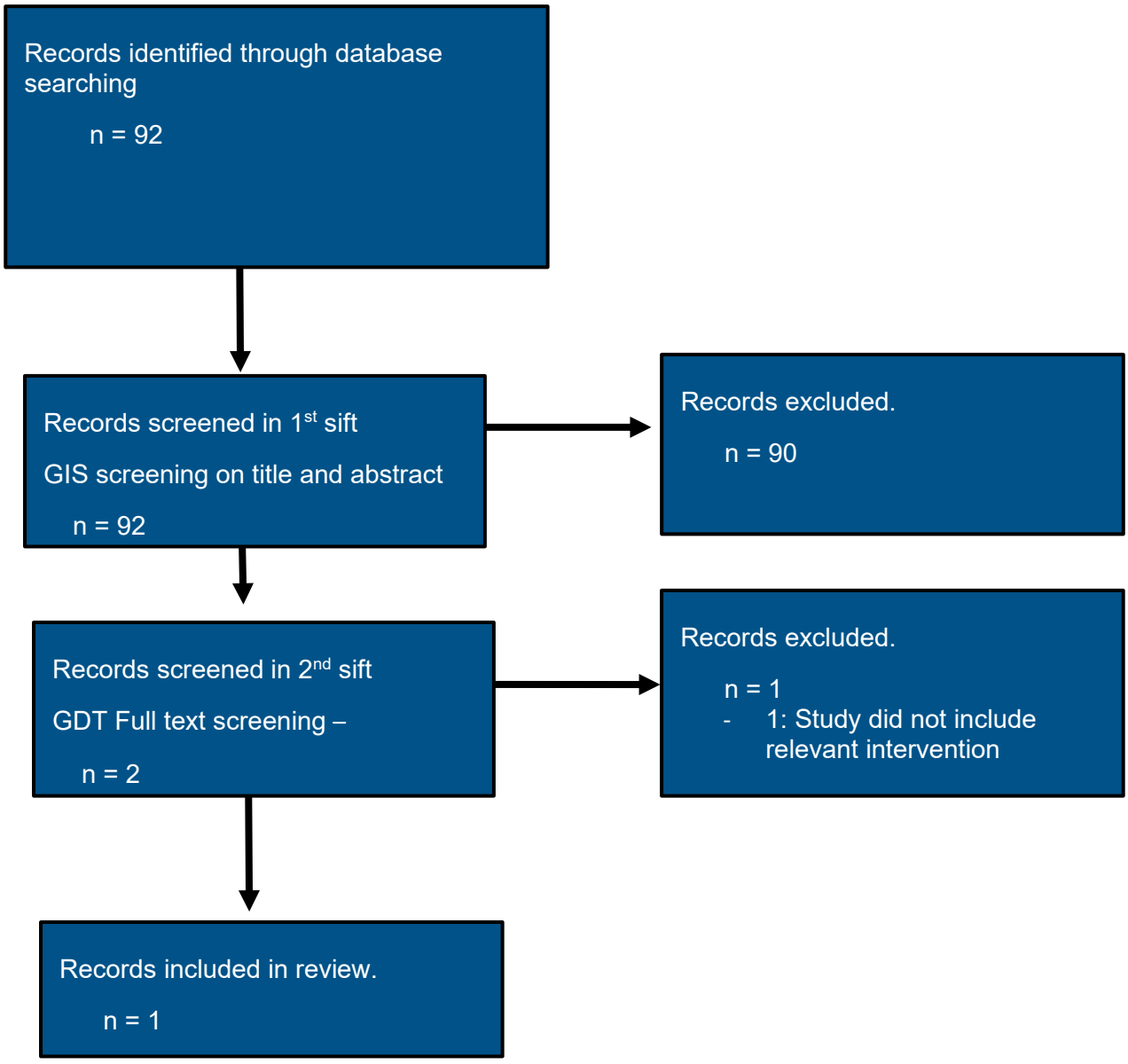
b. No serious concerns – confounders listed in the protocol were accounted for due to the study design (left-right comparison). Baseline severity was not accounted for; however, analyses show that baseline severity was similar in both arms.

c. Not applicable as single-study analysis

d. Very serious concerns as the comparator arm used bath emollients once a week, and outcome measure was not a validated measure

e. Serious concerns as 95% Cis cross one line of the MID

# Appendix G – Economic evidence study selection



# Appendix H – Economic evidence tables

### Table 18: Included economic evidence

| Study | Study type | Study quality | Setting | Intervention | Comparator | Number of participants | Participant characteristics | Methods of analysis | Results | Limitations | Additional comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **BATHE RCT (2018)[2]** | Cost-consequence[3] based on RCT (16- and 52-week endpoints) | Directly Applicable with minor limitations | NHS - Primary and Secondary care | Regular use of bath additives in addition to standard eczema management, which includes the regular application of leave-on emollients and topical corticosteroids when required. | Standard eczema management without any use of bath additives | 257 – Intervention arm<br>213 – comparator arm | Children aged between 12 months and 12 years fulfilling the UK Diagnostic Criteria for Atopic Eczema | The Child Health Utility-9 Dimensions questionnaire were used to estimate utility values for each participant at baseline, 16 weeks and 52 weeks to estimate quality-adjusted life-years (QALYs) gained. CHU-9D is a paediatric quality of life measure that captures issues pertinent to childhood eczema, such as sleep disturbance and the child's mood.<br>Resource-use was collected in Client Service Receipt Inventory (CSRI) questionnaire adapted for the BATHE trial as well as GP records. Unit costs in primary care were derived from Unit Costs of Health | <u>Incremental costs</u><br>**CSRI**<br>16 weeks:<br>- £20.80<br>52 Weeks:<br>- £28.85<br>**GP NR**<br>52 weeks:<br>£14.38<br><u>Incremental QALY</u><br>16 weeks: 0.00<br>52 weeks: 0.00<br>As seen above the incremental QALYs between the bath additive group and no bath additive group were 0 in all analyses.Due to this no ICER could be calculated.<br>The incremental costs show that for costs reported by | The broad spectrum of the age of the children included in the trial was reported to be a limitation when assessing QoL, especially as there are no validated measures to assess the QoL of very young children.<br>The assessment of uncertainty for each measure was estimated and reported in the form of Standard deviations and confidence intervals for point estimates using regression models; | Source of funding: Health Technology Assessment programme |

[2] Santer M, Rumsby K, Ridd MJ, Francis NA, Stuart B, Chorozoglou M, et al. Adding emollient bath additives to standard eczema management for children with eczema: the BATHE RCT. Health Technol Assess 2018;22(57)

[3] The study report described the model as a cost-consequence analysis despite only reporting costs and QALYs. Because the study compares the incremental costs and incremental QALYs associated with the intervention it could also be considered to be a cost-utility analysis. However, it would not be possible to present ICERs as the QALY gain equalled 0 in all groups

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | and Social Care 2016<br>The resource use items from the secondary care data were mainly valued using the NHS Reference Costs for 2015 to 2016.<br><br>The authors used mixed multilevel mixed model framework for costs and outcomes, allowing control of baseline POEM and allowing for clustering of patients within centres.<br><br>Time horizon of 52-weeks.<br>No discounting as <1 year.<br><br>Results found that in addition to bath emollients having no clinical benefit, the use of bath additives does not provide any additional economic or otherwise benefit. | CSRI questionnaire this favoured the use of bath additives, however this did not include intervention costs such as prescription costs, suggesting costs savings in downstream consultation costs. On the other hand, the GP NR reported costs, which did include intervention costs, favoured no bath additives. Based GP NR, the authors concluded bath additives are not cost-effective. | however broad confidence intervals were used for point estimates, therefore increasing uncertainty.<br><br>Exploration of parameter uncertainty was limited, with minimal sensitivity analyses (using CSRI instead of GP NR for resource use, and exploring patient-borne costs). | |

**Table 19: Economic evidence applicability and limitations checklists**

| Study identification |
|---|

| Santer M, Rumsby K, Ridd MJ, Francis NA, Stuart B, Chorozoglou M, et al. Adding emollient bath additives to standard eczema management for children with eczema: the BATHE RCT. Health Technol Assess 2018;22(57) | | |
|---|---|---|
| Category | **Rating** | **Comments** |
| Applicability | | |
| **1.1 Is the study population appropriate for the review question?** | Yes | |
| **1.2 Are the interventions appropriate for the review question?** | Yes | |
| **1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?** | Yes | UK Health and social care perspective taken |
| **1.4 Is the perspective for costs appropriate for the review question?** | Yes | |
| **1.5 Is the perspective for outcomes appropriate for the review question?** | Yes | |
| **1.6 Are all future costs and outcomes discounted appropriately?** | N/A | Costs and effects accrued within a year |
| **1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).** | Yes | QALYs obtained through CHU-9D questionnaire responses (in line with NICE's methods for estimating health-related quality of life in children and young people). |
| **1.8 OVERALL JUDGEMENT** | **DIRECTLY APPLICABLE** | |
| Limitations | | |
| **2.1 Does the model structure adequately reflect the nature of the topic under evaluation?** | N/A | Model is based on study data and does not extrapolate outcomes and costs beyond study period of 52 weeks |
| **2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?** | Yes | Time horizon is appropriate for the study data available, given that there is no more data to extrapolate there is no evidence costs and outcomes could change or have a cumulative effect. |

| | | |
|---|---|---|
| **2.3 Are all important and relevant outcomes included?** | Yes | |
| **2.4 Are the estimates of baseline outcomes from the best available source?** | Yes | |
| **2.5 Are the estimates of relative intervention effects from the best available source?** | Yes | |
| **2.6 Are all important and relevant costs included?** | Yes | |
| **2.7 Are the estimates of resource use from the best available source?** | Yes | Resource use sourced from two sources: Individual patient data and GP electronic records, both of which are validated and used. |
| **2.8 Are the unit costs of resources from the best available source?** | Partly | Costing year reported from 2015-2016 |
| **2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?** | NA | ICER is not reported in this study as not possible to calculate |
| **2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?** | No | The study minimally conducted sensitivity analysis by using two data sources for resource use, however important parameters with uncertainty were not subject to appropriate sensitivity analysis. |
| **2.11 Has no potential financial conflict of interest been declared?** | N/A | |
| **2.12 OVERALL ASSESSMENT** | **MINOR LIMITATIONS** | |

# Appendix I – Health economic model

No original economic model was developed for this guideline.

# Appendix J – Excluded studies

**Table 20: Excluded studies (clinical)**

| Study | Code [Reason] |
|---|---|
| Breternitz, M., Kowatzki, D., Langenauer, M. et al. (2008) Placebo-controlled, double-blind, randomized, prospective study of a glycerol-based emollient on eczematous skin in atopic dermatitis: Biophysical and clinical evaluation. Skin Pharmacology and Physiology 21(1): 39-45 | - Study does not contain a relevant intervention |
| Carbone, A.; Siu, A.; Patel, R. (2010) Pediatric atopic dermatitis: A review of the medical management. Annals of Pharmacotherapy 44(9): 1448-1458 | - Review article but not a systematic review |
| Danby, S, Al Enezi, T, Chittock, J et al. (2011) A randomized comparison of aqueous cream and Oilatum Junior bath additive on skin barrier function in atopic dermatitis. British Journal of Dermatology 165(suppl1): 44-5 | - Conference abstract |
| Danby, S, Al Enezi, T, Chittock, J et al. (2011) A randomized comparison of aqueous cream and Oliatum junior bath additive on skin barrier function in atopic dermatitis. British Journal of Dermatology 165(1): 115 | - Conference abstract |
| Hlela, C., Lunjani, N., Gumedze, F. et al. (2015) Affordable moisturisers are effective in atopic eczema: A randomised controlled trial. South African Medical Journal 105(9): 780-784 | - Comparator in study does not match that specified in protocol |
| Hon, K.L., Kung, J.S.C., Tsang, K.Y.C. et al. (2018) Emollient acceptability in childhood atopic dermatitis: Not all emollients are equal. Current Pediatric Reviews 14(2): 117-122 | - Study does not contain a relevant intervention |
| Hon, Kam Lun, Ng, Wing Gi Gigi, Kung, Jeng Sum C et al. (2019) Pilot Studies on Two Complementary Bath Products for Atopic Dermatitis Children: Pine-Tar and Tea. Medicines (Basel, Switzerland) 6(1) | - Cohort study not adjusted for important confounders |
| Hua, T., Yousaf, M., Gwillim, E. et al. (2021) Does daily bathing or showering worsen atopic dermatitis severity? A systematic review and meta-analysis. Archives of Dermatological Research 313(9): 729-735 | - Systematic review used as source of primary studies |
| Lindh, J.D. and Bradley, M. (2015) Clinical Effectiveness of Moisturizers in Atopic Dermatitis and Related Disorders: A Systematic | - Systematic review used as source of primary studies |

| Study | Code [Reason] |
|---|---|
| Review. American Journal of Clinical Dermatology 16(5): 341-359 | |
| Maarouf, M.; Hendricks, A.J.; Shi, V.Y. (2019) Bathing additives for atopic dermatitis-A systematic review. Dermatitis 30(3): 191-197 | - Systematic review used as source of primary studies |
| Nankervis, Helen, Thomas, Kim S, Delamere, Finola M et al. (2016) Scoping systematic review of treatments for eczema. | - Systematic review used as source of primary studies |
| Ng, W.G.G., Hon, K.L., Kung, J.S.C. et al. (2022) Effect of pine-tar bath on disease severity in moderate-to-severe childhood eczema: an investigator-blinded, crossover, randomized clinical trial. Journal of Dermatological Treatment 33(1): 157-165 | - Comparator in study does not match that specified in protocol |
| Parker, J. and Stevermer, J.J. (2020) Are emollient bath additives beneficial in children with atopic dermatitis?. Evidence-Based Practice 23(8): 47-48 | - Commentary article |
| Rigoni, C.; Cantu, A.M.; Gelmetti, C. (2018) Observational clinical study of a new emollient in 26 patients with atopic dermatitis. European Journal of Pediatric Dermatology 28(4): 218-225 | - Not a relevant study design<br>*Single arm study* |
| Santer, M., Rumsby, K., Ridd, M.J. et al. (2015) Bath additives for the treatment of childhood eczema (BATHE): Protocol for multicentre parallel group randomised trial. BMJ Open 5(10): e009575 | - Secondary publication of an included study that does not provide any additional relevant information |
| Segovia, MJG, Santer, M, Ridd, MJ et al. (2018) Emollient bath additives for the treatment of childhood eczema (BATHE): multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness. Acta pediatrica espanola 76(78): E122-E123 | - Duplicate reference |
| SOMPAYRAC LM and ROSS C (1959) Colloidal oatmeal in atopic dermatitis of the young. The Journal of the Florida Medical Association 45(12) | - Full text paper not available |
| Stuart, B., Rumsby, K., Santer, M. et al. (2018) Feasibility of weekly participant-reported data collection in a pragmatic randomised controlled trial in primary care: Experiences from the BATHE trial (Bath Additives for the Treatment of cHildhood Eczema). Trials 19(1): 582 | - Secondary publication of an included study that does not provide any additional relevant information |

| Study | Code [Reason] |
|---|---|
| Tamura, M., Kawasaki, H., Masunaga, T. et al. (2015) Equivalence evaluation of moisturizers in atopic dermatitis patients. Journal of cosmetic science 66(5): 295-303 | - Study does not contain a relevant intervention |
| van Zuuren EJ, Fedorowicz Z, Christensen R et al. (2017) Emollients and moisturisers for eczema. Cochrane Database Syst Rev 2: CD012119 | - Systematic review used as source of primary studies |
| Waked, I.S. and Ibrahim, Z.M. (2020) Beneficial Effects of Paraffin Bath Therapy as Additional Treatment of Chronic Hand Eczema: A Randomized, Single-Blind, Active-Controlled, Parallel-Group Study. Journal of Alternative and Complementary Medicine 26(12): 1144-1150 | - Study does not contain a relevant intervention |

**Table 21 Excluded studies (economic)**

| Study | Code [Reason] |
|---|---|
| Lee B, W, Detzel P, R. (2015) Treatment of Childhood Atopic Dermatitis and Economic Burden of Illness in Asia Pacific Countries. Annals of Nutrition and Metabolism 66(suppl 1):18-24 | -Study did not contain relevant intervention |

# Appendix K– Research recommendations

The committee did not make any research recommendations as part of this update.

# Appendix L – Methods

### What this guideline covers

This guideline update covers the use of bath emollients in children under 12 years with atopic eczema.

### What this guideline does not cover

For all other areas of the guideline:

- There will be no evidence review as part of this update.
- We will retain the existing recommendations, but we may revise them to ensure consistency. In some cases, minor changes may be made – for example, to update links or bring the language and style up to date – without changing the intent of the recommendation.

### Methods

This guideline was developed using the methods described in the 2018 NICE guidelines manual.

Declarations of interest were recorded according to the NICE conflicts of interest policy.

### Developing the review questions and outcomes

The review questions developed for this guideline were based on the key areas identified in the guideline scope. They were drafted by the NICE guideline development team and refined and validated by the guideline committee.

The review questions were based on the Population, Intervention, Comparator and Outcome [and Study type] (PICO[S]) framework for reviews of interventions.

### Reviewing research evidence

### Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

### Searching for evidence

Evidence was searched for each review question using the methods specified in the 2018 NICE guidelines manual. For details of the search methods see appendix A and appendix B.

### Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 47% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

If systematic reviews (or qualitative evidence syntheses in the case of reviews of qualitative studies) were included in the review protocol, relevant systematic reviews or qualitative evidence syntheses were used to identify any papers not found through the primary search. Based on the small number of records identified through database searching, the decision was taken not to use priority screening, and all records were screened.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

### Methods of combining evidence

### Data synthesis for intervention studies

It was not possible to perform any meta-analyses due to a lack of data. However, where the study reported mean (SD), single study analyses were performed in Cochrane Review Manager V5.3.

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

A mean difference was calculated for continuous outcomes (using the inverse variance method). For continuous outcomes analysed as mean differences, change from baseline values were used in the meta-analysis if they were accompanied by a measure of spread (for example standard deviation). Where change from baseline (accompanied by a measure of spread) were not reported, the corresponding values at the timepoint of interest were used.

### Appraising the quality of evidence

### Intervention studies (relative effect estimates)

RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Non-randomised controlled trials and cohort studies were quality assessed using the ROBINS-I tool. Other study types (for example controlled before and after studies) were assessed using the preferred option specified in the NICE guidelines manual 2018

(appendix H). Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.
- Critical risk of bias (ROBINS-I only) - It is very likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

**Minimally important differences (MIDs) and clinical decision thresholds**

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for the POEM score. Clinical decision thresholds for the POEM outcome of eczema severity are given in Table 22 and are also reported in the relevant evidence reviews. For all other outcomes, default clinical decision thresholds were used.

**Table 22: Identified Clinical decision thresholds**

| Outcome | Clinical decision threshold | Source |
|---|---|---|
| POEM | 3 points | Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy 2012; 67:99-106. doi:10.1111/j.1398-9995.2011. 02719.x<br>Gaunt DM, Metcalfe C, Ridd M. The Patient-Oriented Eczema Measure in young children: responsiveness and minimal clinically important difference. Allergy 2016; 71:1620-5. doi:10.1111/all.12942 |

For continuous outcomes expressed as a mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 standard deviations was used. For SMDs that were back converted to one of the original scales to aid interpretation, rating of imprecision was carried out before back calculation. For relative risks and hazard ratios, where no other clinical decision threshold was available, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used. Odds ratios were converted to risk ratios before presentation to the committee to aid interpretation.

### GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials, non-randomised controlled trials and cohort studies (which were quality assessed using the Cochrane risk of bias tool or ROBINS-I) were initially rated as high quality while data from other study types were initially rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 23. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

**Table 23: Rationale for downgrading quality of evidence for intervention studies**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.<br>Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels |
| Indirectness | Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. |

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| | Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. |
| Inconsistency | Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the $I^2$ statistic.<br>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.<br>Not serious: If the $I^2$ was less than 33.3%, the outcome was not downgraded.<br>Serious: If the $I^2$ was between 33.3% and 66.7%, the outcome was downgraded one level.<br>Very serious: If the $I^2$ was greater than 66.7%, the outcome was downgraded two levels. |
| Imprecision | If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.<br>If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.<br>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios. |
| Publication bias | Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability. |

For outcomes that were originally assigned a quality rating of 'low' (when the data was from observational studies that were not appraised using the ROBINS-I checklist), the quality of evidence for each outcome was upgraded if any of the following three conditions were met and the risk of bias for the outcome was rated as 'no serious':

- Data from studies showed an effect size sufficiently large that it could not be explained by confounding alone.
- Data showed a dose-response gradient.
- Data where all plausible residual confounding was likely to increase our confidence in the effect estimate.

## Reviewing economic evidence

### Inclusion and exclusion of economic studies

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

### Appraising the quality of economic evidence

Economic studies identified through a systematic search of the literature were appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 24.

**Table 24: Applicability criteria**

| Level | Explanation |
|---|---|
| Directly applicable | The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness |
| Partially applicable | The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness |
| Not applicable | The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration |

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 25.

**Table 25: Methodological criteria**

| Level | Explanation |
|---|---|
| Minor limitations | Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness |
| Potentially serious limitations | Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness |
| Very serious limitations | Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration |

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

**Health economic modelling**

## References

Follmann D, Elliott P, Suh I, Cutler J (1992) Variance imputation for overviews of clinical trials with continuous response. Journal of Clinical Epidemiology 45:769–73

Fu R, Vandermeer BW, Shamliyan TA, et al. (2013) Handling Continuous Outcomes in Quantitative Synthesis In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK154408/

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