Emollient bath additives for the treatment of childhood eczema (BATHE): multi-centre pragmatic parallel group randomised controlled trial of clinical and cost-effectiveness

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Title page

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Emollient bath additives for the treatment of childhood eczema (BATHE): multi-centre pragmatic parallel group randomised controlled trial of clinical and cost-effectiveness

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ABSTRACT

Objectives

To determine the clinical and cost-effectiveness of including emollient bath additives in the management of childhood eczema.

Trial design

Pragmatic randomised open-label superiority trial with two parallel groups.

Setting and recruitment

96 general practices in Wales, West of England and Southern England. Invitation by personal letter or opportunistically by usual clinical team.

Participants

Children were eligible to participate if aged over 12 months and less than 12 years, fulfilling UK Diagnostic Criteria for Atopic Dermatitis. Children with inactive or very mild eczema (5 or less on Nottingham Eczema Severity Scale) were excluded, as were children who bathed less than once a week, or whose carers were not willing to accept randomisation. 483 were randomised and one withdrew, leaving 482 children in the trial: 51% female, 84% white, mean age 5 years.

Interventions

The intervention group were prescribed emollient bath additives by their usual clinical team and were asked to use them regularly for 12 months. The control group were asked to use no bath additives for 12 months. Both groups continued with standard eczema management and were given standardised advice on how to wash.

Primary outcome

Eczema control measured by Patient Oriented Eczema Measure (POEM, range 0-28) weekly for 16 weeks.

Secondary outcomes

Eczema severity over 1 year (4-weekly POEM from baseline to 52 weeks); number of eczema exacerbations resulting in primary healthcare consultation; disease-specific quality of life (QOL) (Dermatitis Family Impact); generic QoL (Child Health Utility-9D); resource utilisation; type and quantity of topical corticosteroid/calcineurin inhibitors prescribed.

Randomisation

483 children were randomised (1:1) using online software, stratified by recruiting centre.

Results

96.5% (465/482) of participants completed at least one post-baseline POEM, so were included in the analysis, and 76.8% (370/482) of participants completed questionnaires for more than 80% of the time points for the primary outcome (12/16 weekly questionnaires to 16 weeks).

The mean Baseline POEM was 9.5 (s.d. 5.7) in the bath additives group and 10.1 (s.d. 5.8) in the no bath additives group. The mean POEM over the 16-week period was 7.5 (s.d. 6.0) in the bath additives group and 8.4 (6.0) in the no bath additives group. There was no statistically significant

difference in weekly POEM scores between groups over 16 weeks. After controlling for baseline severity and confounders (ethnicity, topical corticosteroid use, soap substitute use) and allowing for clustering of participants within centres and responses within participants over time, POEM scores in the no bath additive group were 0.41 points higher than in the bath additive group (95% CI -0.27 to 1.10), below the published minimal clinically important difference for POEM of 3 points.

There was no difference between groups in secondary outcomes, economic outcomes or in adverse effects.

Conclusions

This trial found no evidence of clinical benefit from including emollient bath additives in the standard management of childhood eczema. Further research is needed into optimal regimens for leave-on emollient and use of soap substitutes for children with eczema.

Registered on 13th December 2013, ISRCTN: 84102309

What this paper adds

What is already known on this subject

There are three methods of application of emollients: (1) leave-on emollients; (2) soap substitutes; and (3) emollient bath additives (oil and/or emulsifiers designed to be added to bath water).

While there is evidence supporting the use of leave-on emollients and clinical consensus around soap substitutes, there is less agreement regarding the benefits of emollient bath additives for the treatment of childhood eczema.

There have been no adequately powered trials exploring the effectiveness of emollient bath additives in the treatment of childhood eczema.

What this study adds

This large, pragmatic randomised controlled trial of children with eczema (aged 1 to 11 years) recruited through primary care and followed up for 12 months.

We found no evidence of clinically meaningful benefit from emollient bath additives, when used in addition to standard eczema management

Questions remain about optimal regimens for leave-on treatments, soap substitutes and frequency of bathing in eczema.

INTRODUCTION

Childhood eczema (synonyms atopic eczema, atopic dermatitis) is a common condition that can cause substantial impact on quality of life for both the child and their family.(1) Guidelines suggest that 'complete emollient therapy' form the mainstay of treatment for eczema and should be used regularly with topical corticosteroids/calcineurin inhibitors, used in addition for flare-ups.(2)

Emollients are thought to act by providing a barrier over the skin, decreasing moisture loss and protecting against skin irritants. There are three methods of application: (1) leave-on emollients, where emollients are directly applied to the skin; (2) soap substitutes, where emollients are used instead of soap or other wash products; and (3) bath additives, which are oil and/or emulsifiers designed to be added to bath water. Some emollients can be used in more than one way. We therefore use the term 'emollient bath additives' or 'bath additives' rather than 'bath emollients' in order to emphasise the differences between the three methods of application in recognition that products may have more than one method of application.

While there is evidence for the need for leave-on emollients(3) and widespread clinical consensus around soap substitutes, there is less agreement regarding the potential additional benefits of bath additives and there is a dearth of evidence of their effectiveness. Systematic reviews have found no evidence of their effectiveness and one small study suggested they may worsen eczema outcomes.(4) However, bath additives are widely prescribed at a cost of over £23 million per year to the NHS in England.(5)

We sought to determine the clinical and cost-effectiveness of including emollient bath additives in the standard management of childhood eczema.

METHODS

This was a pragmatic, multicentre, randomised open-label superiority trial with two parallel groups allocated in a 1:1 ratio comparing emollient bath additives in addition to standard eczema care versus standard care alone for childhood eczema. The study was registered before recruitment of the first participant, and the study protocol has been published.(6) BATHE was approved by the Newcastle & North Tyneside Research Ethics Committee 1 on 8th May 2014 (Ref: 14/NE/0098)

Children eligible for the trial were aged over 12 months and less than 12 years and fulfilled UK Diagnostic Criteria for Atopic Dermatitis.(7) Children with inactive or very mild eczema over the last 12 months were excluded, defined as a score of 5 or less on Nottingham Eczema Severity Scale (scale from 3 to 15, where 3 to 8 is mild; 9 to 11 is moderate; and 12 to 15 is severe).(8) Children who usually bathed less than once a week or whose carers were not willing to accept randomisation were also excluded. Only one child was enrolled per family.

Participants were recruited from 96 general practices in Wales, West of England and Southern England. We used practices' medical records to identify children who had a recorded diagnosis of eczema and who had obtained one or more prescriptions for eczema in the past 12 months. General practice staff also recruited potential participants opportunistically. Parents/carers were asked to return a reply slip to the study team. A brief screening questionnaire included the UK Diagnostic Criteria for Atopic Dermatitis and the Nottingham Eczema Severity Scale. A researcher telephoned parents/carers who expressed an interest in the study to confirm likely eligibility and arrange a baseline appointment at which time informed consent was sought and baseline questionnaires were completed. Subsequent questionnaires were completed online or by post with no further face-to-

face contact between the participants and the trial team. Informed consent was received for trial participants prior to enrolment.

Interventions

The intervention group were prescribed bath additives by their GP surgery and were asked to use them regularly for 12 months. We encouraged practices to issue Oilatum (Glaxo SmithKline), Balneum (Allmarall Ltd) or Aveeno (Johnson & Johnson Ltd) bath additives, which are the most frequently prescribed products in the UK. Other bath additives could be issued, with the exception of products containing antimicrobials, which were excluded as they have been shown to have greater irritant effect than other bath additives.(9) The control group were not prescribed bath additives and were asked not to use any bath additives for 12 months. Both groups were given standardised written advice on how to wash, including the use of leave-on emollient as soap substitute. Both groups were advised to continue with standard eczema management, including regular leave-on emollients and topical corticosteroids when required. On-going clinical care was otherwise unchanged.

Outcomes

The primary outcome was eczema severity measured by Patient Oriented Eczema Measure (POEM) reported by parent/carer weekly over 16 weeks.(10, 11) The POEM is a patient-reported outcome which scores symptoms over the previous week. It consists of seven questions which can be completed by the child's parent or carer and provides a severity score on a scale from 0 to 28, where 0 to 2 is clear/almost clear; 3 to 7 is mild; 8 to 16 is moderate; and 17 to 28 is severe.(11) The published minimal clinically important difference of the POEM is 3 points.(12, 13) POEM was the only patient-reported outcome measure for eczema to demonstrate validity and repeatability in a systematic review and has been adopted as the preferred patient-reported outcome measure for eczema symptoms internationally.(14, 15)

The relapsing and remitting nature of eczema means that repeated measures is a better reflection of effect than follow-up assessment at a single timepoint.

Secondary outcomes included

- Eczema severity measured by POEM every 4 weeks from baseline to 52 weeks
- Disease-specific quality of life at 16 weeks and 1 year, measured by Dermatitis Family Impact(16)
- Generic quality of life at 16 weeks and 1 year, measured by Child Health Utility 9D(17)
- Number of eczema exacerbations resulting in a primary healthcare consultation over 1 year (GP notes review)
- Type (strength) and quantity of topical corticosteroid/calcineurin inhibitors prescribed over 1 year (GP notes review)
- Resource use from GP notes review and parent/carer questionnaires

Other outcomes:

- Adherence to treatment allocation (parent/carer report)
- Adverse effects, such as stinging, redness, slipping or bath refusal (parent/carer report)

Sample size

The sample size was calculated for repeated measures ANOVA in weekly POEM scores over 16 weeks. Using weekly data from a similar population in the SWET trial(18) we aimed to detect a mean difference of 2.0 (s.d. 7.0) between intervention and control groups. Although the published minimal clinically important difference for POEM is 3,(12, 13) we sought to detect a difference of 2 due to the expectation of low POEM scores at baseline in a population recruited entirely through primary care. An alpha of 0.05 and power 0.9 gave a sample size of 338. Allowing for 20% loss to follow-up gave a total sample size of 423 participants.

Early data showed that approximately 80% of participants in both groups reported adherence to treatment allocation. Therefore, in order to allow a per protocol analysis with 90% power, in addition to the primary intention to treat analysis, we sought and obtained approval for an ethics amendment requesting permission to recruit an additional 68 participants, giving a revised target of 491 participants. There were no other protocol changes.

Randomisation

Participants who provided consent were randomly allocated in 1:1 ratio to the intervention or control groups, stratified by co-ordinating centre (Southampton, Bristol, Cardiff). Randomisations were conducted at the end of the recruitment appointment, following completion of consent and baseline questionnaire so that treatment allocation could not be known prior to study entry.

Randomisation was carried out using LifeGuide software hosted at the University of Southampton and automated to ensure concealment. As baseline appointments were sometimes remote from internet access, a back-up randomisation system involved phoning the trial manager. Unique participant identifier was then entered into a spreadsheet that allocated treatment on a 1:1 ratio, stratified by co-ordinating centre, from a MS Excel spreadsheet pre-programmed by the Trial Statistician. 30 randomisations were conducted using this offline method.

It was not possible to make a convincing placebo for emollient bath additives, which add a greasy film to water, and participating families were therefore not blind to treatment allocation. As all outcomes were either participant-reported or collected on clinical record review template, we did not mask Clinical Study Officers/Research Nurses to allocation. Statisticians carrying out the analyses were blind to treatment allocation.

Statistical methods

Analysis was conducted according to CONSORT guidelines, following an analysis plan agreed in advance with the independent Trial Steering/Data monitoring Committee. We used descriptive statistics to compare baseline characteristics of trial participants by allocated group. The primary analysis for the total POEM score was performed using a multilevel mixed model framework with observations over time from weeks 1 through to 16 (level 1) nested within participants (level 2). Our primary outcome is based on adjusted results, controlling for baseline POEM, recruiting centre and any significant confounders. We also report unadjusted results.

For all models, participants were analysed in the group to which they were randomised, regardless of their adherence to that allocation (intention to treat analysis). The only exception to this was the per-protocol analysis, where analyses were carried out on the basis of bath additive use as reported by parent/carer.

For the analysis of secondary outcomes, repeated measures analysis in line with that used for the primary outcome was used for the monthly POEM measure up to 1 year. For other secondary outcomes, linear regression was used for continuous outcomes if the assumptions were met. Otherwise non-parametric analyses were used. Logistic regression was used for dichotomous outcomes and a suitable count model, as determined by goodness of fit measures, for count data. All analyses controlled for stratification variables and potential confounders. Pre-planned sensitivity analysis and exploratory subgroup analyses were carried out as set out in the Statistical Analysis Plan. The economic evaluation used resource use, cost and effectiveness data collected from participants and GP notes review.

Patient and public involvement (PPI)

The James Lind Alliance Priority Setting Partnership for Eczema top 10 included priorities around bathing/washing and around the best ways to use emollients.(19) This trial was funded by NIHR Health Technology Assessment commissioned call following a topic suggestion form submitted through their website.

The trial management group included an experienced PPI co-applicant (AR) who participated in all phases of trial design, including planning recruitment and recruitment materials. Members of the Centre of Evidence Based Dermatology Patient Panel were also consulted at trial design stage and additional PPI representation was also sought when planning how to disseminate findings. The independent trial steering committee included a PPI member.

The results will be emailed to all trial participants and published on the trial website.

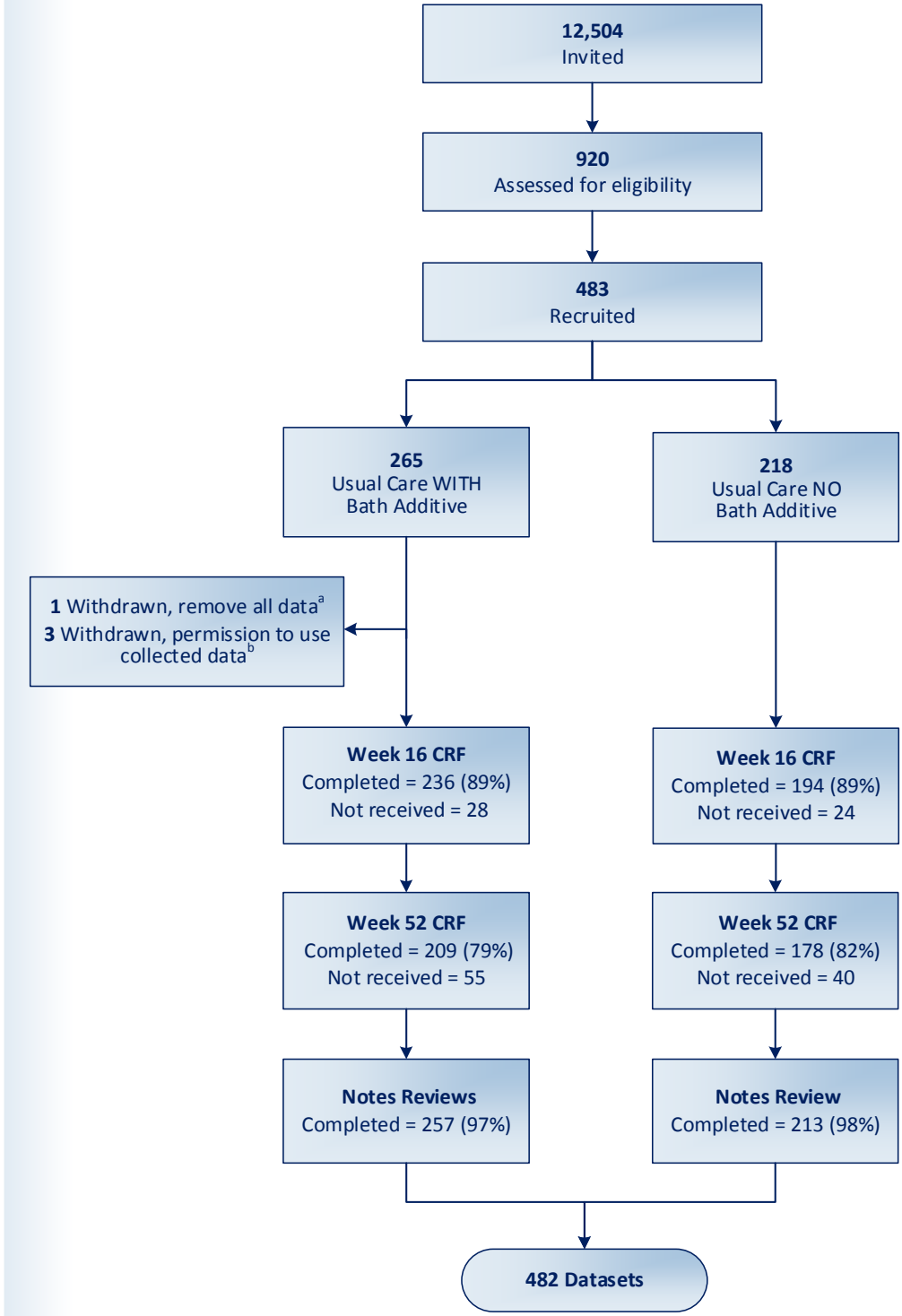
The burden of the intervention was minimal, with many families already familiar with using bath additives and no difficulty

RESULTS

Participants were recruited between December 2014 and May 2016. Invitations were sent to the parents/carers of 12,504 children and 1,451 responses were received. Of these, 920 expressed a willingness to be contacted and included a completed screening questionnaire. 662 met eligibility criteria and were approached regarding participation and 483 entered the trial. One carer subsequently withdrew permission so analysis was carried out on data from 482 participants (n = 264 intervention group, n = 218 control group) (see Figure 1).

Table 1 shows the characteristics of participants in the trial. It can be seen that they were well balanced at baseline, although there were more participants allocated to the bath additive group than the no bath additive group.

Figure 1:



[a] reported eczema had not been a problem for some time, although screening form clearly indicated eligibility

[b] one parent wished to bathe two children together but felt bath additive was worsening the symptoms of the child not enrolled in the study; one was finding improvement with new creams and, despite reassurance, did not wish this to affect the study results; one child was withdrawn by their GP after experiencing a rash.

Table 1: Baseline characteristics of trial participants

		Bath additive (n=264)	No bath additive (n=218)	Total (n =482)
Child age (years)				
	Mean (s.d.)	5.4 (2.9)	5.2 (2.9)	5.3 (2.9)
Child gender				
	Male	138/264 (52.3%)	100/218 (45.9%)	238/482 (49.4%)
	Female	126/264 (47.7%)	118/218 (54.1%)	244/482 (50.6%)
Carer age (years)				
	Mean (s.d.)	36.5 (6.5)	35.9 (6.7)	36.2 (6.5)
Carer gender				
	Male	11/258 (4.3%)	12/212 (5.7%)	23/470 (4.9%)
	Female	247/258 (95.7%)	200/212 (94.3%)	447/470 (95.1%)
Ethnicity				
	White	228/257 (86.0%)	176/215 (81.9%)	397/472 (84.1%)
	Black	6/257 (1.9%)	9/215 (4.2%)	15/472 (3.2%)
	Asian	15/257 (5.8%)	16/215 (7.4%)	31/472 (6.6%)
	Mixed race	10/257 (3.9%)	9/215 (4.2%)	19/472 (4.0%)
	Chinese	2/257 (0.8%)	3/215 (1.4%)	5/472 (1.1%)
	Other	3/257 (1.2%)	2/215 (0.9%)	5/472 (1.1%)
Highest qualification				
	Not answered	6/257 (2.3%)	3/213 (1.4%)	9/470 (1.9%)
	Degree or equivalent	106/257 (41.3%)	90/213 (42.3%)	197/470 (41.7%)
	Diploma or equivalent	56/257 (21.8%)	37/213 (17.4%)	95/470 (19.8%)
	A-level	25/257 (9.7%)	24/213 (11.3%)	49/470 (10.4%)
	GSCE/O-level	50/257 (19.5%)	38/213 (17.8%)	88/470 (18.7%)
	Other	12/257 (4.7%)	16/213 (7.5%)	29/470 (6.0%)
	None	2/257 (0.8%)	5/213 (2.4%)	7/470 (1.5%)
Cost of Living				
	Not answered	7/257 (2.7%)	3/213 (1.4%)	10/470 (2.1%)
	Finding it a strain	11/257 (4.3%)	3/213 (1.4%)	14/470 (3.0%)
	Have to be careful	105/257 (40.9%)	82/213 (38.5%)	187/470 (39.8%)
	Able to manage	99/257 (38.5%)	90/213 (42.3%)	189/470 (40.2%)
	Quite comfortable	35/257 (13.6%)	35/213 (16.4%)	70/470 (14.9%)
Prior belief in bath additives (1-9)[a]		5.1 (2.2)	4.8 (2.3)	5.0 (2.3)
POEM scores				
	Mean (sd)	9.5 (5.7)	10.1 (5.8)	9.8 (5.8)
	Mild (0-7)	114 (43.2%)	73 (33.5%)	187 (38.8%)
	Moderate (8-16)	119 (45.1%)	114 (52.3%)	233 (48.3%)
	Severe (17-28)	31 (11.7%)	31 (14.2%)	62 (12.9%)
DFIQ score				
	Median (IQR)	2 (1,6)	3 (1,7)	3 (1,7)
NESS score				
	Mean (sd)	9.5 (2.3)	9.5 (2.3)	9.5 (2.3)
CHU-9D score (Utility values)				
	Mean (sd)	0.90 (0.1)	0.90 (0.1)	0.90 (0.1)

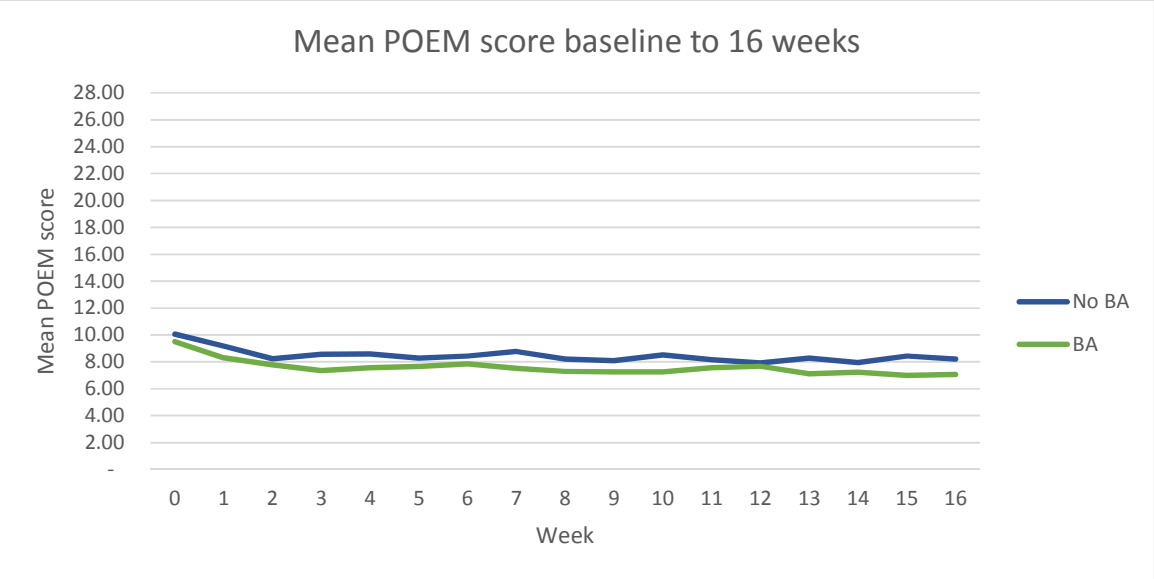
[a] where 1 is 'not at all effective' and 9 is 'very effective'

465/482 (96.5%) participants had completed at least one POEM following baseline and were included in the primary analysis, and 76.8% (370/482) completed more than 80% of the time points for the primary outcome (12/16 weekly questionnaires to 16 weeks).

Parent/carer report of adherence to treatment allocation group at 16 weeks showed 92.7% (216/233) of participants in the bath additive group using bath additive 'every time' (73.8% (172/233)) or 'more than half the time' (18.9% (44/233)). Similarly, 92.1% (176/191) of those in the no bath additive group said that they used bath additive either 'never' (87.4% (167/191)) or 'less than half the time' (4.7% (9/191)).

The Baseline POEM score was 9.5 (s.d. 5.7) in the bath additives group and 10.1 (s.d. 5.8) in the no bath additives group. The mean POEM score over the 16 week period was 7.5 (s.d. 6.0) in the bath additives group and 8.4 (6.0) in the no bath additives group. There was no statistically significant difference in weekly POEM scores between the two groups over the 16-week period. After controlling for baseline severity and confounders (ethnic group, topical corticosteroid use, and soap substitute use) and allowing for the clustering of participants within centres and responses within participants over time, the POEM score in the no bath additive group was 0.41 points higher than in the bath additive group (95% CI -0.27 to 1.10), which is substantially lower than the published minimal clinically important difference of 3 points.(12, 13)

Figure 2: POEM scores during the 16-week primary outcome period



Secondary analyses looking at differences between groups based on adherence to treatment allocation (per protocol analysis) similarly showed no statistically significant difference between the groups on POEM 16 weeks repeated measures: 'More than half' or 'every time' vs. 'less than half the time' or 'never' adjusted difference in mean POEM 0.32 (95% CI -0.37 to 1.02).

There were no significant differences between groups in any of the secondary outcomes, such as POEM over 52 weeks (adjusted difference in mean POEM 0.75 (95%CI -0.05 to 1.55), Dermatitis

Family Impact, generic quality of life (Child Health Utility 9D), number of eczema exacerbations and type /quantity of topical corticosteroid/calcineurin inhibitors prescribed over 1 year.

Table 2: Secondary outcomes by treatment allocation

	Bath additive Mean (s.d.)	No bath additive Mean (s.d)	Univariate difference in mean POEM (95% CI)	Adjusted difference in mean POEM (95% CI)
Secondary outcome – Monthly repeated measures				
Over the 52 week period (repeated measures)	7.3 (6.3)	8.4 (6.4)	0.99 (0.03 to 1.96)	0.75 (-0.05 to 1.55)
Secondary outcome – Disease-specific QOL	**Bath additive Median (IQR)**	**No bath additive Median (IQR)**	**Univariate difference in median DFIQ (95% CI)**	**Adjusted difference in median DFIQ (95% CI)**
DFIQ at baseline	2 (1,6)	3 (1,7)		
DFIQ at 16 weeks	2 (0,5)	3 (1,7)	1.00 (0.09 to 1.91)	0.29 (-0.57 to 1.14)
DFIQ at 52 weeks	2 (0,5)	2 (0,6)	0.00 (-0.93 to 0.93)	-0.29 (-1.36 to 0.79)
Secondary outcome – quantity of TCS/TCI prescribed				
Total number of TCS/TCI prescriptions	325	346		
Median number of TCS/TCI prescriptions	0 (0,2)	1 (0,3)		
Secondary outcome – Exacerbations			**Univariate RR exacerbations (95% CI)**	**Adjusted RR (95% CI)**
Number of exacerbations	1 (0,2)	1 (0,3)	1.33 (1.02 to 1.75)	1.24 (0.96 to 1.60)

Adverse effects were remarkably similar in both groups, despite slips in the bath, stinging or redness being common side effects reported in Summary of Product Characteristics for emollient bath additives. Over the first 16 weeks, 34.5% in the bath additive group and 35.4% in the no bath additive group reported at least one adverse event on weekly questionnaires (Table 3), with no statistically significant difference between the groups (OR 1.40 95% CI 0.79 to 2.47).

Table 3: Adverse events by treatment allocation

Adverse events – 16 weeks	Bath additive	No bath additive
Slips	44 (17.5%)	52 (24.8%)
Stinging	4 (1.6%)	4 (1.9%)
Redness	35 (13.9%)	48 (23.0%)
Refuses a bath	21 (8.3%)	25 (12.0%)

Adverse events – 52 weeks	Bath additive	No bath additive
Slips	56 (22.2%)	63 (30.1%)
Stinging	7 (2.8%)	4 (1.9%)
Redness	44 (17.5%)	61 (29.2%)
Refuses a bath	30 (11.9%)	31 (14.8%)

The economic evaluation followed a pre-specified analysis plan and explored resource utilisation from the health system (NHS) and family perspective. The mean annual costs to the NHS were estimated at £180.50 (s.d. 237.0) for the bath additives group and £166.12 (s.d. 293.0) for the no bath additives group. Similarly, the annual results for QALYs were 0.91 (s.d. 0.1) and 0.90 (s.d. 0.1) for the bath additives and the no bath additives group respectively. The difference in cost means was £14.38 (95% CI -33.45 to 62.21) and in QALY means was 0.00 (95% CI -0.01 to 0.02). The family-borne costs showed an annual higher spend within the no bath additives group of £51.37 (95% CI -15.74 to 118.49) and the adjusted difference was £47.56 (95% CI -18.07 to 113.19), none statistically significant. The economic analysis found no benefits that could be used to consider the intervention cost-effective.

DISCUSSION

This trial provides strong evidence that emollient bath additives provide minimal or no additional benefit beyond standard eczema care in the management of childhood eczema.

The BATHE trial was an adequately powered trial, with high follow-up rates and good adherence to trial intervention allocations. The study has strong external validity as it was pragmatic in design to reflect normal practice, and participants were broadly reflective of children with eczema seen in primary care. We used a participant-reported outcome measure with good validity that has been accepted by international consensus.(15) A participant-reported outcome could be biased in favour of finding a positive effect of trial intervention due to a perception of benefits of treatment. However, the negative result of the trial suggests that this was not the case.

This is the largest trial on the role of emollient bath additives to date and previous reviews of the literature have not been able to draw conclusions from existing small trials.(4)

These findings are timely for clinicians and prescribing advisers, as prescribing guidelines vary widely in their advice regarding bath additive use(20) and pressure on budgets have led to formularies becoming increasingly restrictive. Reviews have estimated that bath additives may contribute to up to a third of the costs of eczema in the UK.(21) Our findings provide evidence that can contribute to effective prescribing in this area, where there is currently very little research evidence to guide decision-making. These findings are also useful for families with eczema as they have more certainty about directing their efforts towards more effective treatments.

Our findings are only relevant to the use of emollient bath additives. More research is needed into optimal regimens for other emollients, although there is strong evidence that regular use of leave-on emollients prevents flare-ups in eczema(3) and there is widespread clinical consensus around the role of emollients as soap substitutes.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS or the Department of Health.

Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation other than the NIHR for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement:

e.g. "Data sharing: patient level data [and/or] full dataset [and/or] technical appendix [and/or] statistical code [and/or] available at [/doi] [with open access/with these restrictions] [from the corresponding author at]. Participants gave informed consent for data sharing [or ... consent was not obtained but the presented data are anonymised and risk of identification is low ... or consent was not obtained but the potential benefits of sharing these data outweigh the potential harms because ...]". If no such further data are available, please use this wording: "Data sharing: no additional data available."

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Contributorship

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